American Heart Journal

VOL. 37 MAY, 1949 No. 6

Original Communications

OBSERVATIONS ON THE ANATOMY OF THE ATRIOVENTRICULAR BUNDLE (BUNDLE OF HIS) AND THE QUESTION OF OTHER MUSCULAR ATRIOVENTRICULAR CONNECTIONS IN NORMAL HUMAN HEARTS

ALBERT D. KISTIN, M.D.
WASHINGTON, D. C.

ACCORDING to the present most widely accepted view, the impulse to contraction in the human heart is conducted from the atria to the ventricles by way of a single muscular atrioventricular bundle (bundle of His) located at the cephalic end of the interventricular septum. The bundle originates in a distinct atrioventricular node (node of Tawara) lying on the right side of the interatrial septum a short distance ventral to the coronary sinus. The atrioventricular node has a number of connections with myocardial fibers of the right atrium. The cardiac impulse is believed to originate in the sinoatrial node located at the junction of the superior vena cava and the right auricle. The atrioventricular bundle divides into two branches, right and left, which descend on the respective sides of the interventricular septum. The anatomic basis for this concept has been established through the studies of a number of investigators.[1-26] By analogy with what has been observed in sheep and bovine hearts, it is believed that each bundle branch forms a widespread subendocardial network in man, but this has not been demonstrated. In sheep and bovine hearts a tough sheath surrounds the atrioventricular bundle, and dye injected within the sheath passes out to the finest branches of the terminal network in the ventricles outlining a complex atrioventricular fiber system.[27-33] In the human heart, however, there is no sheath about the atrioventricular bundle and heretofore, attempts at demonstration by dye injection have failed.

Glomset and Glomset[34,35] and Glomset and Birge[36] have questioned the entire concept of the muscular atrioventricular conduction system. Among the conclusions of these authors concerning the human heart are the following:

Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

From the Cardiovascular Research Unit, Veterans Administration, Washington, D. C.

(1) the bundle of His is inconstant; (2) there are no muscular connections between the bundle of His and the right atrium; (3) the bundle of His does not bifurcate and, therefore, has no left branch; (4) there is no distinct node of Tawara; and (5) there are many atrioventricular connections in various regions of the heart. These authors find no anatomic basis for the myogenic theory of cardiac conduction. They find a well-developed intrinsic nervous system in the heart which they believe must be taken into account for an understanding of cardiac conduction.

These conclusions require serious consideration. If they are correct, it becomes necessary to revise accepted physiologic concepts including much of the theoretical basis of electrocardiography and the interpretation of abnormal rhythms and heart block. In the present study these conclusions were not confirmed, but instead the observations are in accord with the more generally accepted view of the anatomy of the human atrioventricular node and the atrioventricular bundle and its branches.

THE "PURKINJE FIBERS" AND METHODS OF STUDY

In 1845, Purkinje[37] described distinctive fibers in the hearts of sheep and other animals. Compared with ordinary myocardium, these fibers are considerably larger, their myofibrils are much sparser, and the cross striations are less distinct. The nuclei lie within a prominent clear region of sarcoplasm and the myofibrils tend to be arranged near the periphery. Tawara's great contribution[4] was the demonstration that the bundle described by His and the fibers described by Purkinje were parts of a single atrioventricular system. He showed that the bundle of His divided into two branches, each of which could be followed a relatively long distance down the septum and which expanded into complex fiber networks, the components of which were histologically identical in some animals with the fibers described by Purkinje. It is important to point out that Tawara recognized substantial histologic differences between the component fibers of the atrioventricular systems of different animals. He found that the microscopic characteristics of the fibers of man and dog were quite different from those of sheep; that they were much less distinctive and more nearly resembled ordinary myocardium.

Against this historical background it may be easier to evaluate two different methods that have been used to look for an anatomic basis for a myogenic conduction system in man and to appreciate two different implications of the term, "Purkinje fiber." Some investigators have searched sections of various parts of the human heart for fibers with the microscopic characteristics of the fibers first seen by Purkinje in sheep.[38,39] It is sometimes assumed that human conducting fibers must have this microscopic structure, and that all fibers with this structure are necessarily conduction fibers. From this point of view, the criterion for a "Purkinje fiber" is its microscopic appearance.

A different method of study has been to identify the muscular atrioventricular bridge in serial sections. Investigators who used this method[4,8,10,21,23] agreed that in man there is an atrioventricular node and an atrioventricular bundle and

branches in exactly the same anatomic location and with the same anatomic relationships as in other animals. They observed, on the other hand, that the histologic structure of the components of this atrioventricular fiber system in man is generally quite different from that of the sheep. From this second point of view the term "Purkinje fiber" often refers to the fiber components of the muscular atrioventricular conduction system without any commitment regarding special microscopic structure. Investigators using this method of study accept the proposition that homologous structures may become histologically different in different animals and still serve similar functions.

A recent study of the human moderator band[39] illustrates very well the difference between the two points of view. Since the course of the right bundle branch has previously been described along the moderator band, the authors sought here "Purkinje fibers" by microscopic criteria. They describe such fibers and state that there are numerous connections between them and adjacent myocardium. However, other investigators who have traced the human right branch in serial sections from the atrioventricular bundle state that its microscopic structure is indistinguishable from that of adjacent myocardium, and that it can be traced all the way to the base of the anterior papillary muscle of the right ventricle as a distinct muscle bundle without giving off any branches to adjacent myocardium.[21,22] Obviously the two groups of investigators are not describing the same thing.

In the present study the method of serial sections was employed, for it seemed to be the most reliable method. In considering theories of conduction of the cardiac impulse the important question is whether a muscular bridge exists between atria and ventricles, without any prior assumptions concerning special structural characteristics of such a bridge.

MATERIAL AND METHODS

Microscopic Studies.—The hearts of three adults and one newborn infant were studied. Except for slight to moderate coronary arteriosclerosis in the adult hearts, all four were anatomically normal. The electrocardiograms of two of the adults recorded shortly before death showed no conduction disturbances or other abnormalities. In the other two cases electrocardiograms were not obtained.

Blocks were cut and numbered in sequence around the atrioventricular orifice. Each block consisted of the entire thickness of atrium (or interatrial septum) and ventricle (or interventricular septum) and included a portion of atrium above the fibrous atrioventricular ring and a portion of ventricle below the ring (except the blocks including the part of the mitral valve attached to the aorta, which, of course, contained no ventricular portion below). A small portion of valve was left attached to the atrioventricular junction. The plane of cutting was approximately in a radius of the atrioventricular orifice and perpendicular to the atrioventricular ring. The sections were 10 microns thick and were stained by Masson's method,[40] which differentiates connective tissue (stained blue) from muscle (stained pink to red).

From two of the adult hearts serial sections were prepared from blocks completely encircling both atrioventricular orifices. These included sections from the regions of the interatrial septum and the upper part of the interventricular septum where the atrioventricular node, the bundle of His, and the origins of the bundle branches have been observed. The location of these structures is fully discussed and illustrated in the text to follow. From the third adult heart serial sections were prepared from blocks completely encircling the mitral orifice, and, in addition, serial sections were prepared for location of the atrioventricular node, the bundle of His, and the origins of the bundle branches. Every tenth section of the series was mounted and studied. By every tenth section being mounted, the usual gap between studied sections was 0.09 millimeter. Some of the sections mounted were unsuitable for study, producing a number of larger gaps in the series. A single poor section between two good ones enlarged the gap to 0.19 mm.; two consecutive poor sections, to 0.29 mm.; and three consecutive poor sections, to 0.39 millimeter. There were a number of gaps 0.19 mm. thick in all three adult hearts. There was one gap 0.29 mm. thick in the heart in which the mitral ring was studied. In one of the hearts in which both rings were studied there were two gaps of 0.29 mm. and two others of 0.39 millimeter.

From the heart of the newborn infant a series of sections was prepared for the study of the atrioventricular node, the atrioventricular bundle, and the origins of the bundle branches. In this series every section was mounted and studied. There were no gaps thicker than 30 microns. In addition, series in which each section was mounted and studied were prepared from a number of regions about both atrioventricular orifices, although these did not constitute complete series about either orifice.

Macroscopic Studies.—Dissections of more than forty human hearts were carried out under a binocular dissecting microscope. A magnification of seven times was found to be very satisfactory; it provided adequate magnification and at the same time was not so great as to obscure relationships. Most of the hearts were examined after fixation in formalin, but a number also were examined unfixed soon after removal at autopsy.

SERIAL SECTIONS OF THE ATRIOVENTRICULAR NODE (NODE OF TAWARA), THE ATRIOVENTRICULAR BUNDLE (BUNDLE OF HIS), AND THE ORIGINS OF THE BUNDLE BRANCHES

The atrioventricular node appears as a distinct structure in microscopic sections (Figs. 1 and 3,*A*). It is a compact mass of interlacing, fine muscle fibers, the shape of an ovoid in cross section. It is found a short distance ventral to the coronary sinus and just above the attachment of the medial cusp of the tricuspid valve. One side of the node is separated from the endocardium of the right atrium by a thin layer of subendocardial atrial muscle and a variable amount of fat. The opposite side lies against the central fibrous body. The smallest dimension is between these two sides. The approximate maximum dimensions of the node in the three adult hearts are: dorsoventral, 3.6, 4.2, and 4.1 mm.; cephalocaudal, 4.0, 4.5, and 3.0 mm.; and thickness, 0.5, 1.0, and 0.75 millimeter.

The individual fibers of the atrioventricular node are thinner than the adjacent atrial fibers and stain slightly paler. The dense tangle of thin muscle fibers that constitutes the node is quite well demarcated from the surrounding looser arrangement of coarser atrial fibers. There are, however, in each case a number of connections of the atrial fibers with the fibers of the node (Figs. 1 and 3,*A*). In one of the hearts these are mostly in the cephalic and dorsal parts of the node. In the other hearts in addition to connections in these locations there are also a number of connections on the side of the node beneath the endocardium and in the caudal part of the node. A large artery is seen in the nodes

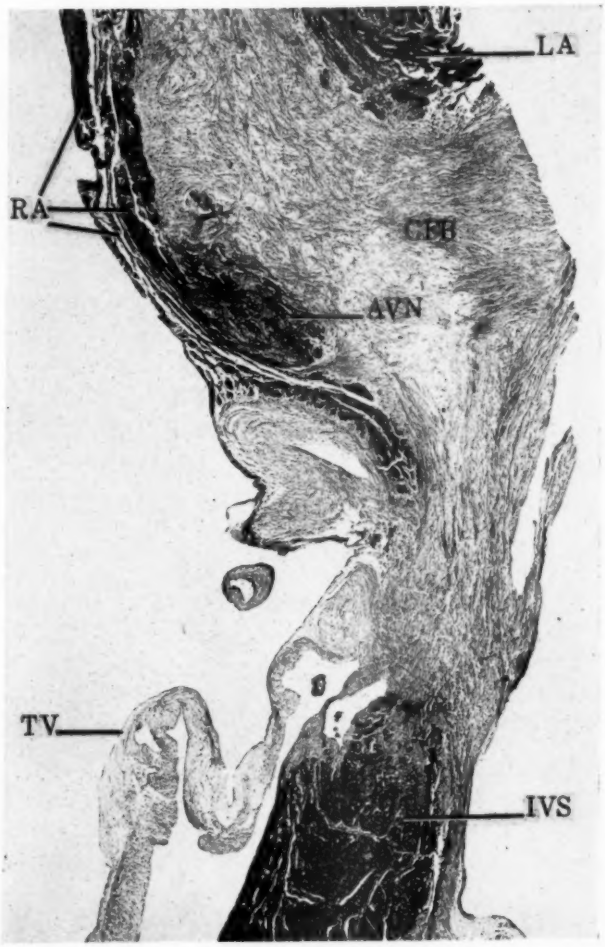


Fig. 1.—Photomicrograph of section from normal heart of newborn infant (× 17.8), Masson stain. *AVN*, atrioventricular node (node of Tawara); *CFB*, central fibrous body; *IVS*, myocardium of interventricular septum; *LA*, myocardium of left atrium; *RA*, myocardium of right atrium; *TV*, tricuspid valve. The connection of the node with the myocardial fibers of the right atrium is apparent. As in the other hearts studied, the structure designated here as atrioventricular node is seen to be continuous in serial sections with a distinct atrioventricular bundle which divides into two branches (see Fig. 3).

of the adult hearts and just to one side of the node of the heart of the newborn infant. In the node of the latter in addition to interlacing fibers there are regions of compact cellular masses.

The atrioventricular node is directly continuous ventrally with the bundle of His which can be traced section by section from the node through the central fibrous body and the membranous portion of the interventricular septum. The bundle lies in close association with the uppermost border of the muscular portion of the interventricular septum, although its exact relations vary somewhat in the different hearts (Fig. 2). In one adult heart the bundle, triangular in cross section, lies above the crest of the muscular portion of the interventricular septum throughout its extent (Fig. 2,*A*). In the other two adult hearts and in the heart of the newborn infant the dorsal portion of the bundle lies above the crest of the septum, but the ventral portion comes to lie on the left side of the septum (Fig. 2,*B*).

The shapes of the sections of the bundle vary in the different hearts and at different levels in the same heart. They are oval, roughly triangular, roughly quadrilateral, and entirely irregular. The intensity of staining of the bundle is slightly less than that of the adjacent myocardium. The individual fibers of the bundle are somewhat larger than those of the atrioventricular node but still smaller than the bulk of myocardial fibers forming the adjacent interventricular septum. There is a rapid transition from the interlacing network of the atrioventricular node to a more or less parallel arrangement of fibers in the bundle itself.

The division of the bundle is clear in all four hearts. The three-dimensional image obtained from tracing the serial sections is much more convincing than the few illustrations that can be shown (Fig. 3). The left branch is given off as a thin sheet of fibers seen on edge in the sections (Figs. 2 and 3), and the right branch seems to be a continuation of the bundle itself (Fig. 3). In three of the hearts the bifurcation is very close to the crest of the muscular portion of the interventricular septum, so that the branches descend immediately to the subendocardial regions of the respective sides of the septum. In one case, however, the bifurcation occurs on the left side of the septum some distance below the crest so that the right branch must penetrate a thickness of muscle in the upper part of the interventricular septum to reach its subendocardial position.

In the heart of the newborn infant a small strand is given off from the bundle a short distance after its origin from the atrioventricular node and before the division of the bundle into left and right branches. This strand descends into the muscular portion of interventricular septum and soon joins septal myocardial fibers. Similar connections have previously been described.[41,42] In the adult hearts small strands are given off from the atrioventricular bundle in a comparable location, but these seem to end in the central fibrous body without joining septal myocardium. It must be remembered that in the adult hearts only every tenth section of the series was studied, and the possibility of fusion of these small strands with septal myocardium in locations between the studied sections cannot be definitely excluded.

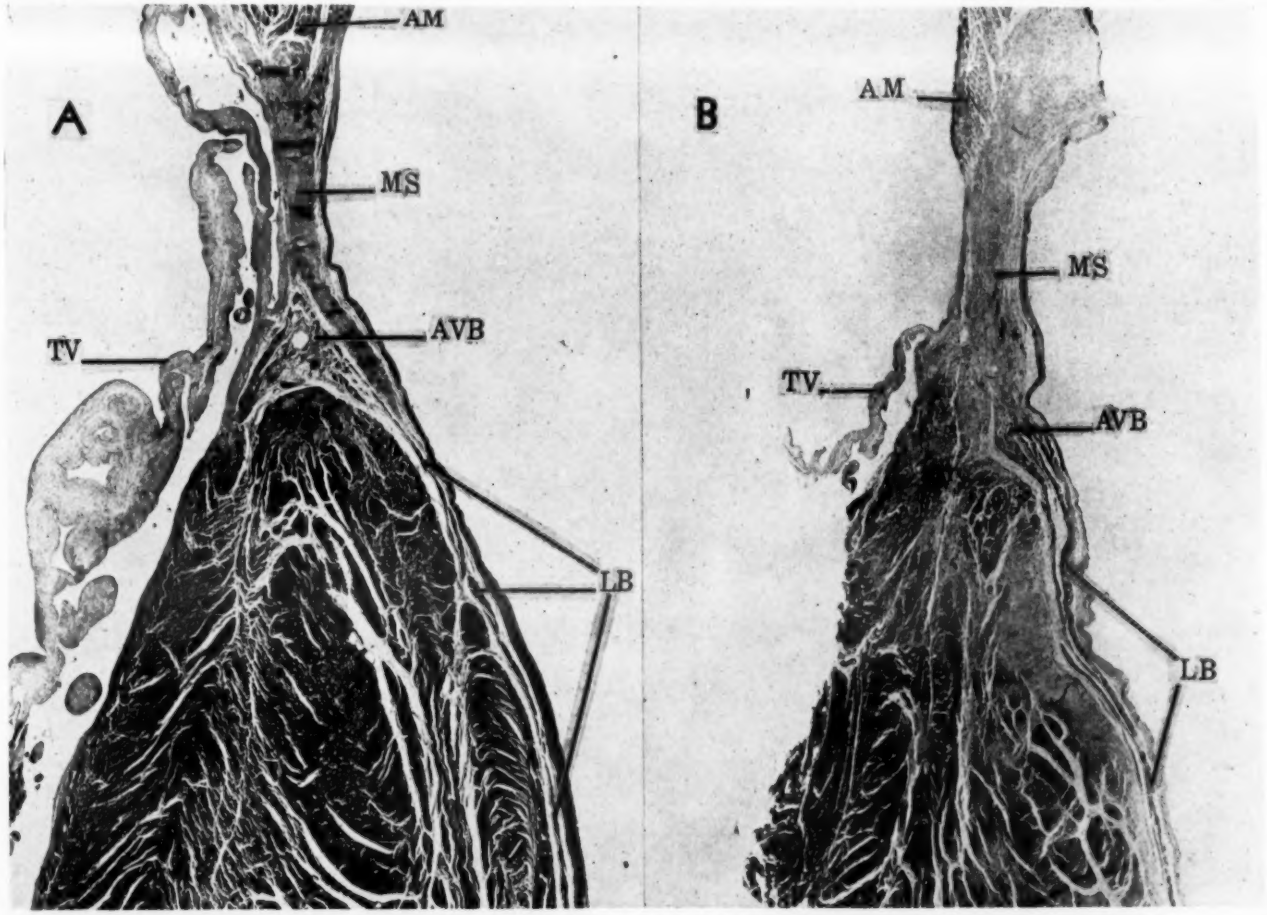


Fig. 2.—Photomicrographs of sections from two normal adult human hearts, showing the atrioventricular bundle (bundle of His) and its left branch (× 9.6). Masson stain. *AM*, atrial myocardium; *AVB*, atrioventricular bundle (bundle of His); *IVS*, myocardium of interventricular septum; *LB*, left branch of bundle; *MS*, membranous portion of interventricular septum; *TV*, tricuspid valve. The bundle shown in *A* lies within the membranous septum and could be readily exposed in dissection by an approach from either side of the septum. The bundle shown in *B*, however, lies below the membranous septum and is separated from the endocardium of the right side of the septum by a thickness of myocardium; exposure from the right side in this case would be more difficult than from the left.

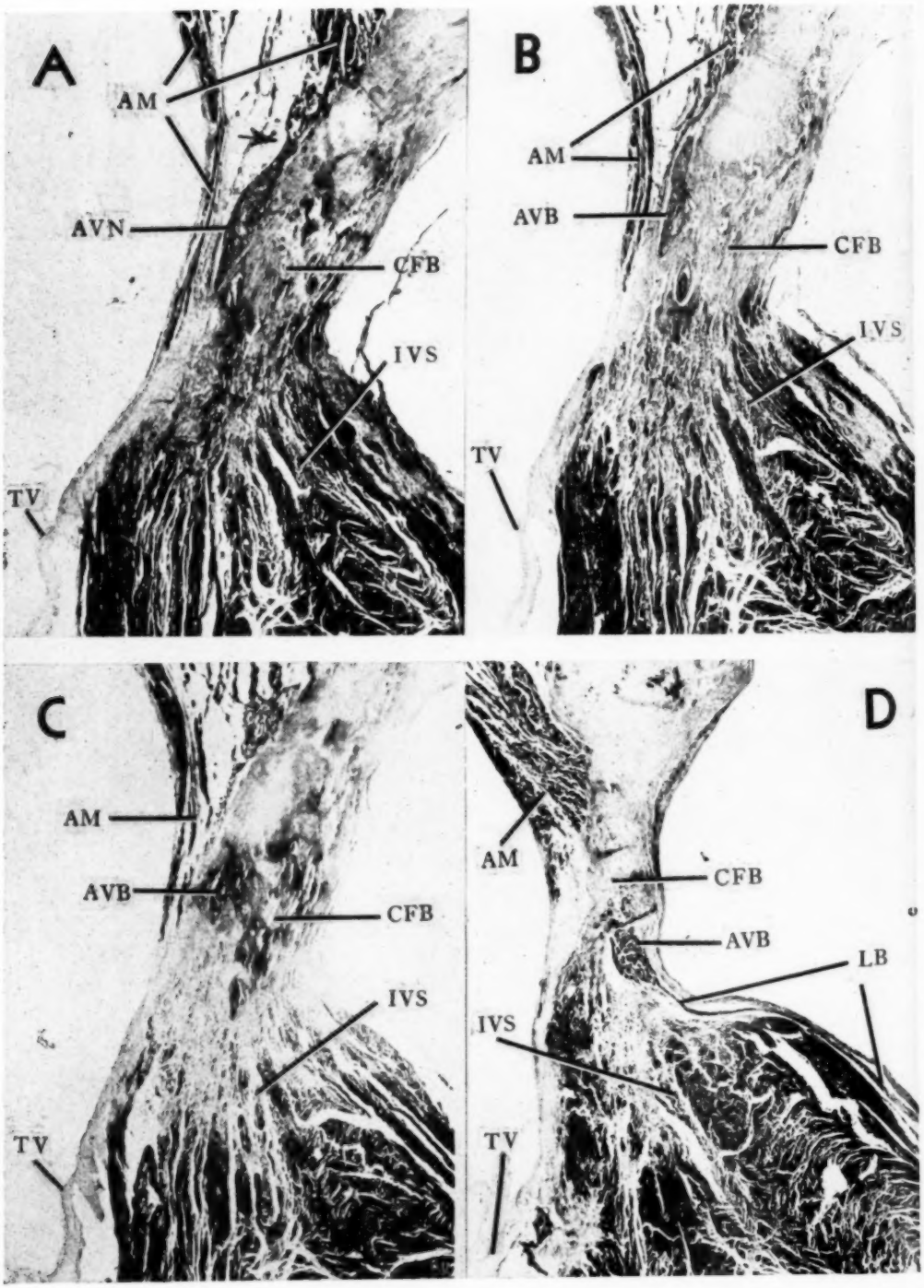


Fig. 3. *A D. See opposite page for legend.*

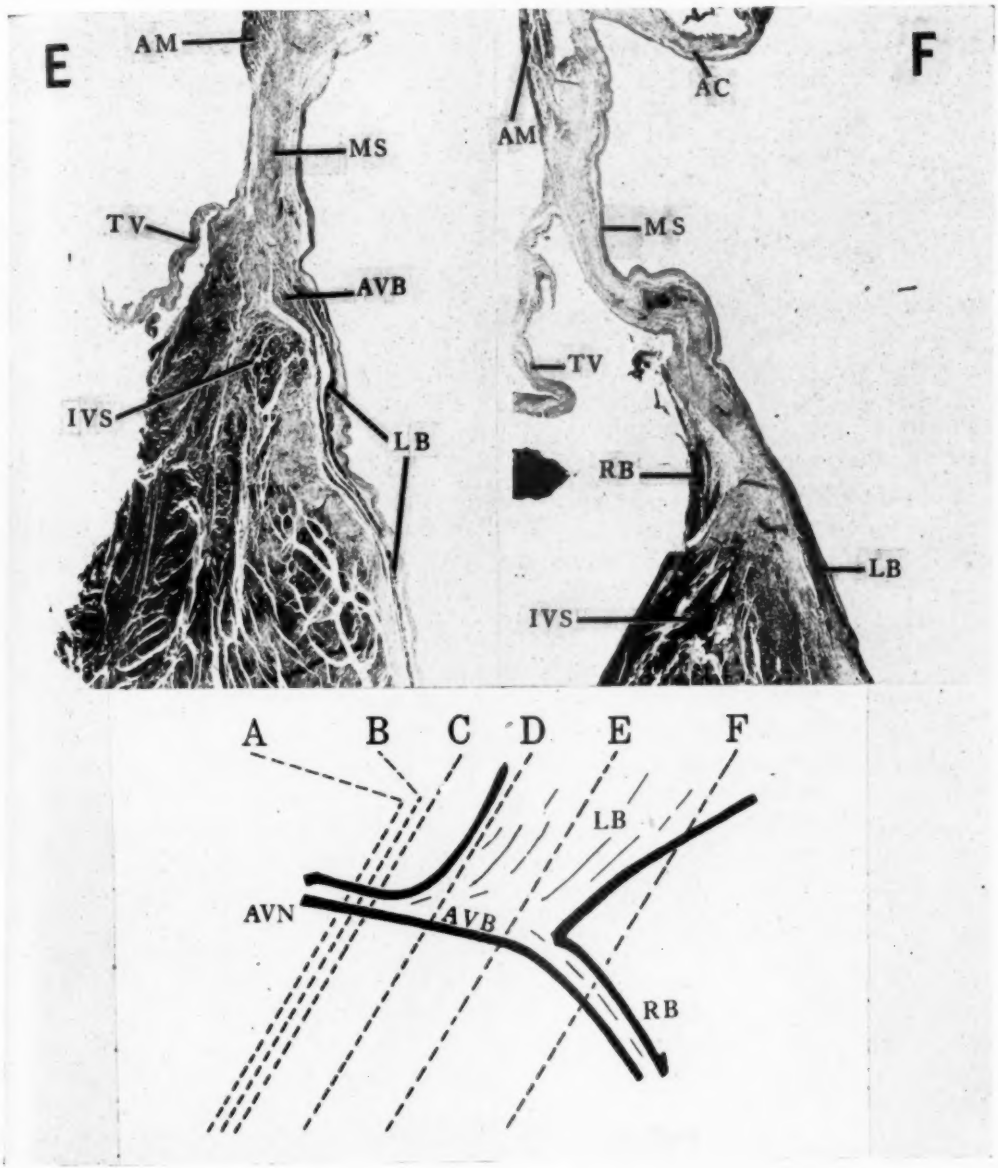


Fig. 3.—*A* to *F*, Photomicrographs of representative sections from a consecutive series from a normal adult human heart (× 8.3), Masson stain. *AC*, cusp of aortic valve; *AM*, atrial myocardium; *AVB*, atrioventricular bundle (bundle of His); *AVN*, atrioventricular node (node of Tawara); *CFB*, central fibrous body; *IVS*, myocardium of interventricular septum; *LB*, left branch of bundle; *MS*, membranous portion of interventricular septum; *RB*, right branch of bundle; *TV*, tricuspid valve. There is direct continuity in the serial sections from atrioventricular node to atrioventricular bundle to bundle branches. The arrow in *A* points to connections of right atrial myocardium with the superior part of the atrioventricular node. The diagram shows the approximate levels of Sections *A* to *F* with reference to the atrioventricular node, the atrioventricular bundle, and the origins of the bundle branches seen from above. For orientation of the diagram in the heart, compare with Figs. 4 and 5. The distances of the sections from *A* are: *B*, 0.4 mm.; *C*, 0.8 mm.; *D*, 2.6 mm.; *E*, 5.1 mm.; and *F*, 8.6 millimeters.

The right branch can be traced section after section as a distinct muscle bundle. Soon after its origin from the bundle its fibers are indistinguishable on the basis of microscopic structure and staining characteristics from adjacent fibers of the interventricular septum.

The intensity of staining and thickness of the individual fibers of the left branch vary considerably. Near its origin from the bundle some of its fibers are more slender and stain paler than the other fibers of the myocardium and resemble the fibers of the atrioventricular bundle. Other fibers stain more deeply and are larger, resembling septal myocardial fibers. Still other fibers are larger than the adjacent septal fibers and contain large, clear, unstained regions within which the nucleus may be situated. The latter fibers fit to a large extent the description given for the "Purkinje fibers" of sheep, but this microscopic picture is not limited to fibers of the left branch for it is occasionally observed in other myocardial fibers which have no connection with the atrioventricular bundle or its branches so far as can be determined in serial sections. The variations in structure and staining within the left branch are sometimes observed along the length of a single muscle fiber. That is, a slender, paler-staining segment of a fiber may become continuous with a larger, more deeply staining segment; or a clear, unstained swelling appears in the course of a slender fiber. Sometimes a number of slender fibers fuse to form the large, clear segments.

It has been suggested that some of the cytologic features observed are due to artefacts.[24] In the present study this factor cannot be evaluated since the hearts were obtained in the usual manner at post-mortem examination, and there was a delay up to several hours between death and fixation of the organs.

MACROSCOPIC STUDIES

Some of the structures under discussion were demonstrated by naked-eye dissection by Retzer,[2] Keith and Flack,[5] Curran,[9] Robertson,[12] Holl,[13] Tandler,[14] Walmsley,[19] Yater, Osterberg, and Hefke,[20] and Walls.[26] De Gaetani[11] believed that the structures were inconstant. Holmes,[17] Mahaim,[21] and Evans[24] stated that naked-eye dissection was not possible. Yater,[20] in order to obtain relatively fresh specimens for microchemical analysis, found it possible to dissect the atrioventricular bundle within a few minutes in a large percentage of the hearts of adults. In the present study, by dissections carried out under a binocular microscope at a magnification of seven times, the bundle of His and the right branch were demonstrated in thirty-five of forty consecutive attempts. These forty dissections were carried out after preliminary studies to establish relationships and technique. In most of these dissections the origin of the left branch and the site of bifurcation were demonstrated as well.

The crucial landmark for dissection is the boundary between the membranous and muscular portions of the septum. A small segment of the medial cusp of the tricuspid valve must be removed to expose this region on the right side. On the left side this region is immediately below and between the posterior and right aortic cusps.

The Atrioventricular Bundle (*Bundle of His*).—The examination was usually begun on the right side. In some hearts the bundle may be seen without magnification and without dissection. It then appears as a whitish band in the lower part of the translucent membranous septum. In one heart it formed a round bulge in this region. Where the bundle is not immediately apparent the fibrous tissue at the boundary between membranous and muscular septa is carefully teased away. In most cases this exposes the bundle lying either entirely within the lower part of the membranous septum or partly in the membranous septum and partly on the muscular septum.

Under the discussion of the serial sections the variability of the exact location of the bundle was described (Fig. 2). In the dissections a better appreciation of this variability is obtained. In some cases the bundle lies on the left side just beneath the crest of the muscular septum, so that the approach from the right side may fail to expose it. The bundle illustrated in Fig. 2,*B* is an example. While the bundle lies superficially beneath the endocardium of the left side of the septum it is below the membranous septum and separated from the endocardium of the right side of the septum by a considerable thickness of myocardium and fibrous connective tissue. In cases like this the bundle is revealed by teasing away the superficial tissue of the uppermost part of the left side of the muscular septum.

Even when the bundle lies entirely within the membranous septum, the exposure from one side may be easier than from the other. The membranous septum varies considerably in thickness and is sometimes quite tough. In some cases the bundle is superficial on one side of a thick, tough, membranous septum, whereas exposure from the other side necessitates tearing away a considerable thickness of resistant fibrous tissue. It is advisable to examine both sides of the septum carefully and to proceed with the dissection cautiously until the most desirable approach is established.

In both fixed and fresh hearts the bundle is paler than the adjacent myocardium. In fixed hearts it is gray, white, or pale yellow, whereas in fresh hearts it often has a pale pink or violet hue. In some fresh hearts fine vessels may be seen to accompany the bundle. The commonest shape of the bundle is a more or less flat band with the thin dimension perpendicular to the face of the septum. Sometimes it is more rounded and thicker so that it would be oval on cross section. Occasionally it is roughly prismatic with one side lying on top of the muscular portion of the interventricular septum. The width of the bundle varies from approximately 0.7 to 3.5 mm., with an average of 1.8 millimeters. Since there is no sharp demarcation of the bundle where it blends with right atrial myocardium (see below), measurements of its length can only be approximate. Measured as well as possible from the most dorsal point where the bundle could be described as a distinct entity to the point of bifurcation (see below), the length of the atrioventricular bundle ranges between 7.0 and 15.0 mm., with an average of 11.3 millimeters.

The bundle may be traced back dorsally through a variable extent of membranous septum and then through the central fibrous body, or it may be followed into the latter directly from the upper part of the muscular septum. The central

fibrous body is often very tough and almost cartilaginous. When the bundle is traced backward or dorsally in this manner it is seen that it definitely crosses the line of attachment of the medial cusp of the tricuspid valve and passes into the right atrium. To follow it further in the right atrium a thin covering layer of subendocardial atrial muscle must usually be removed. There may be some fat in this region. The bundle definitely blends with the right atrial tissue in the region just above the attachment of the medial cusp of the tricuspid valve and a short distance ventral to the coronary sinus (Fig. 4).

The failure to demonstrate the atrioventricular bundle in a few of the dissections may be attributed to the inherent technical difficulties or possibly to unrecognized anatomic variations. Except for its possible rare absence as a congenital anomaly the bundle seems to be a constant structure.

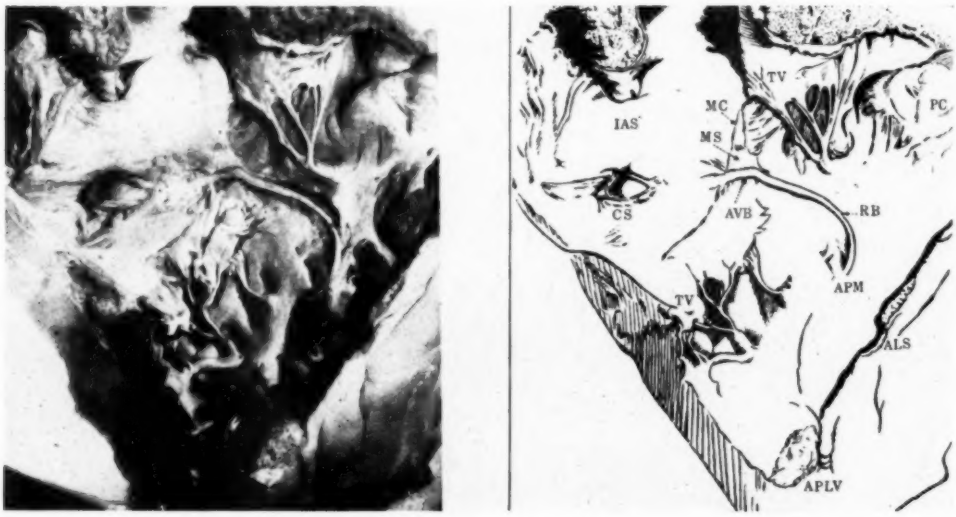


Fig. 4.—Photograph and labeled diagram of dissection of the atrioventricular bundle (bundle of His) and right branch of normal adult human heart (approximately × ¾). Looking into the right ventricle and facing the right side of the interventricular septum. *ALS*, anterior longitudinal sulcus; *APLV*, apex of left ventricle; *APM*, base of anterior papillary muscle or right ventricle; *AVB*, atrioventricular bundle (bundle of His); *CS*, orifice of coronary sinus; *IAS*, interatrial septum; *MC*, line of attachment of medial cusp of tricuspid valve; *MS*, membranous portion of interventricular septum; *PC*, cusp of pulmonary valve; *RB*, right branch of atrioventricular bundle; *TV*, medial cusp of tricuspid valve. A part of the medial cusp of the tricuspid valve which covered the membranous septum and the bundle has been removed.

The Atrioventricular Node (*Node of Tawara*).—Demonstration of the atrioventricular node as a structure with more or less clearly defined boundaries was possible in only a few dissections. The failure to demonstrate a sharply delimited node in most instances by the method of dissection used must be correlated with a study of the serial sections. It was demonstrated in the serial sections that when viewed in cross section the node appears as a distinct entity (Figs. 1 and 3,*A*). In the dissection, however, one looks down on the subendocardial side of the node, and here apparently there is usually no sharp demarcation at the sites of blending with atrial muscle and bundle of His. This may be appreciated

to some extent by examining Fig. 1. If one imagines approaching this node from the endocardium by dissection, one can see how the subendocardial side of the node might be perfectly flush with adjacent atrial myocardium. The circumscribed character of the node is more apparent in a plane perpendicular to that viewed in the dissection, a plane such as is illustrated in Figs. 1 and 3,*A*. The side of the node itself may be marred in being exposed, since in removing the subendocardial atrial muscle that covers it, connections between it and the subendocardial muscle must be torn.

The Right Branch.—The bundle can be traced ventrally directly into the right branch (Fig. 4). The latter may be followed in a curved course on the right side of the septum from its origin to the base of the anterior papillary muscle. The muscle of the septum along which the right branch runs is often raised into a ridge of variable prominence which is known as the septal trabecula or moderator band. The proximal portion of the right branch is usually immediately subendocardial. After a short distance it gradually comes to lie deeper in the myocardium. The most distal visible portion becomes superficial again near the base of the anterior papillary muscle and frequently widens and fans out. Like the bundle, the right branch is paler than the adjacent myocardium. It often looks very much like a fine nerve after it is exposed by dissection. The bundle and right branch were always visible to the naked eye after exposure. In some cases, however, they were extremely thin, particularly the right branch, and in these cases it is doubtful if exposure would have been possible by dissection without magnification.

The proximal part of the right branch and the most distal part grossly demonstrable are often visible without magnification and without dissection. From 1.5 to 2.9 mm. of the distal part was visible in various hearts where it appeared as a thin, gray subendocardial band or streak passing toward the base of the anterior papillary muscle. In one heart the entire right branch was visible without magnification and without dissection.

In most cases the right branch is given off from the bundle near the crest of the muscular septum and comes to lie subendocardially immediately. However, in a few instances in which the bundle lay on the left side of the septum and the bifurcation was below the crest of the septum, the right branch had to be traced through the muscle of the upper part of the interventricular septum.

The right branch is usually a more or less rounded, narrow band with the cross section of a flattened oval or circle. In some of the hearts the distal part of the right branch was inadvertently cut by the pathologist in opening the heart, and in these hearts the branch can usually be followed to the cut end. In practically all of the remaining hearts in which the branch had not been cut it can be followed as far as the base of the anterior papillary muscle where it can be traced no farther. In the latter hearts the distance that the right branch can be followed from the point of bifurcation of the atrioventricular bundle (see below) ranges from 23.0 to 50.0 mm., with an average of 38.9 millimeters. The width of the right branch varies from approximately 0.3 to 2.7 mm., with an average of 1.0 millimeter. Usually the branch is wider at its origin and then narrows down.

Sometimes the terminal visible portion at the base of the anterior papillary muscle widens out again.

The Left Branch and the Bifurcation.—The dissection of the bifurcation and the beginning of the left branch is best carried out after the bundle of His and the right branch have been exposed. The best approach is from above. The structures above the bundle are carefully cut away, and the septum is mounted under the microscope in such a way that one is looking down on the crest of the septum. If the tissue on the left side of the bundle is now carefully teased away from above downward, it can be demonstrated in most cases that the bundle sends off a series of fibers or a very thin sheet of muscle to the left side of the septum. When the dissection is successfully carried far enough ventrally along the upper part of the septum a distinct inverted V can be made out, one arm of which is formed by the right branch and the other by the ventral margin of the left branch (Fig. 5). The apex of the V was taken as the point of bifurcation in measuring the lengths of the bundle of His and of the right branch. Actually, fibers of the left branch are given off for some distance dorsal to this point, in one case over a distance of as much as 9.0 millimeters. The V is usually near the ventral margin of the membranous portion of the interventricular septum.

While the origin of the left branch is quite distinct and the branch could be followed for a short distance, it was not possible to dissect it very far down the septum without tearing it. The left branch is thinner than the right. Its fibers are intimately connected with the endocardium, and they tear easily when an attempt is made to separate them from the endocardium. It was not possible to expose the entire left bundle branch and its divisions as illustrated in one of the standard anatomy texts.[43]

THE QUESTION OF ACCESSORY ATRIOVENTRICULAR MUSCULAR CONNECTIONS

At the height of the controversy between the proponents of the neurogenic and the myogenic theories at the end of the last century, Kent's study on atrioventricular muscular connections in mammalian hearts appeared.[44,a] It was the first demonstration of such connections and described them in several regions of the hearts of various newborn and older animals. His,[1] in a study which appeared immediately following that of Kent in the same year, described and localized the single atrioventricular muscular bundle which now bears his name. Kent maintained in later papers that the concept of a single atrioventricular connection was erroneous, that there were other atrioventricular connections besides the bundle of His, and that, in particular, there was one in the right lateral portion of the human heart.[44,a-g] The latter has become known as the bundle of Kent. Other investigators have stated also that there are multiple atrioventricular connections.[34,38]

A thorough search for atrioventricular muscular connections requires the study of large numbers of serial sections. Three such detailed studies have recently been made of human hearts in cases in which the electrocardiogram showed the syndrome of anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome). In one case Wood, Wolferth, and Geckeler[45] found several

atrioventricular connections in the general region designated by Kent. In the second case, Oehnell[46] found no muscular connections between the right atrium and right ventricle, but did locate an atrioventricular bundle in the posterior wall of the heart connecting the left atrium and left ventricle. In the third case, Deerhake, Kimball, Burch, and Henthorne[47] found one connection on the right side of the heart and one on the left.

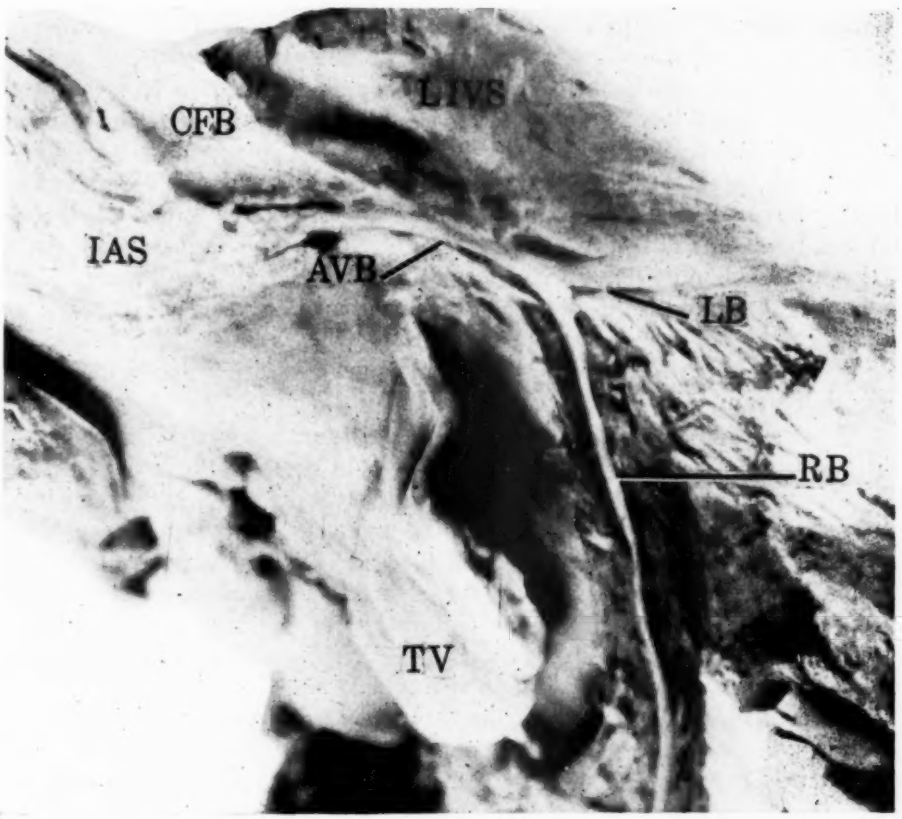


Fig. 5.—Photograph of dissection of atrioventricular bundle (bundle of His) and its bifurcation, normal adult human heart, (approximately × 4). Looking down on the crest of the interventricular septum. The structures above the crest of the septum have been removed. *AVB*, atrioventricular bundle (bundle of His); *CFB*, central fibrous body; *IAS*, interatrial septum; *LB*, left branch of atrioventricular bundle; *LIVS*, left side of interventricular septum; *RB*, right branch of atrioventricular bundle; *TV*, medial cusp of tricuspid valve.

In the present investigation the atrioventricular junctions of four normal human hearts were carefully searched by serial sections, in two of the hearts completely around both atrioventricular orifices, in a third completely around the mitral orifice, and in a fourth in a number of regions about both atrioventricular orifices. In none of the hearts were any muscular atrioventricular connections found other than the bundle of His. The atrial and ventricular muscle fibers are sometimes very close to each other at the atrioventricular junction, but they are

always separated by a layer of fibrous tissue of varying thickness, and careful study of serial sections reveals no continuity of muscle fibers from atrium to ventricle. It is possible that by studying only every tenth section in the adult hearts some small connections were overlooked. It is possible, also, that because of scattered, unsatisfactory sections in both the adult and the newborn hearts such small connections were overlooked. Nevertheless, in the thousands of sections studied no evidence of accessory muscular connections was found.

Anomalous Atrioventricular Excitation (Wolff-Parkinson-White Syndrome).—These observations may have some bearing on one of the hypotheses which has been advanced to explain the syndrome of anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome). It has been postulated that this syndrome arises from the existence of anomalous atrioventricular muscular pathways through which premature excitation of the ventricle occurs.[48] While such connections have been histologically demonstrated in a few cases of this syndrome,[45,46,47] it has not been entirely clear whether such connections exist also in the hearts of individuals with normal atrioventricular conduction. If these connections are found to be absent in most normal human hearts, then a normal control for the hypothesis will be available. The presence of accessory connections in the cases of anomalous atrioventricular excitation would then assume added importance.

To be sure, the hypothesis is still tenable if accessory atrioventricular connections are found more frequently than only in cases of the Wolff-Parkinson-White syndrome, provided that the connections are always found with the syndrome. It may be maintained that the accessory pathways are necessary to produce the syndrome, but that they do not always function, and that their mere presence, therefore, does not insure the existence of anomalous atrioventricular conduction. The hypothesis must, in fact, postulate that the pathways sometimes do not function since in individuals with the Wolff-Parkinson-White syndrome, anomalous conduction may be apparent only at times, and at other times conduction may be normal. Admittedly, however, the hypothesis would be more convincing if the anomalous connections were absent in most normal hearts and were invariably associated with the syndrome. Much further investigation will be required to determine whether or not this is so.

Another type of possible accessory pathway which may conceivably be involved in anomalous atrioventricular excitation is one from the atrioventricular node or bundle directly to septal myocardium, by-passing the main bundle branches. Such connections were observed by Mahaim[41] and by Robb and Turman,[42] and one was present in the heart of the newborn infant reported here. How frequent such connections are and what their significance is requires much further investigation. They have not been mentioned in the few cases of anomalous atrioventricular excitation in which histologic studies were carried out.

Nerve Elements.—In many regions widely distributed about both atrioventricular rings, nerve ganglion cells and nerves were observed at the atrioventricular junction. The extrinsic and intrinsic nerve supplies of the hearts of man and other animals have been studied by several investigators.[22,36,49-58] By

suitable techniques some of these investigators traced nerve endings to myocardial fibers as well as to the sinoatrial node, the atrioventricular node, and the bundle of His. The nervous influence on atrioventricular conduction, particularly the vagal influence, is very well known, and the demonstrated nerve endings in the nodes and bundle have generally been regarded as serving the function of modifying the activity of the muscular atrioventricular conduction system.

It is not within the scope of this paper to consider the experimental and pathologic evidence for and against the myogenic and neurogenic theories of cardiac conduction. The object of this study has been simply to examine the contention that there is no anatomic basis for the myogenic theory.[35] Evidence has been presented which corroborates the opinion of most students of the subject that there is a sound anatomic basis for the myogenic theory of atrioventricular conduction.

SUMMARY AND CONCLUSIONS

1. The widely accepted concept of the atrioventricular muscular conduction system of the human heart has recently been challenged. The present microscopic and macroscopic studies do not confirm the anatomic observations on which the criticism is based.

2. As has been demonstrated by previous investigators, there is normally a constant atrioventricular muscular bundle (bundle of His) located at the cephalic end of the interventricular septum which originates in a distinct atrioventricular node (node of Tawara) and divides into left and right bundle branches. The atrioventricular node has a number of connections with atrial muscle. These relations are described and illustrated.

3. A systematic search in a few normal hearts fails to reveal any atrioventricular muscular connections other than the bundle of His.

4. The syndrome of anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome) has been explained by the existence of accessory atrioventricular muscular connections through which premature ventricular excitation occurs. This hypothesis has been supported by the histologic demonstration of such connections in a few cases, but there is inadequate information about normal hearts for comparison.

5. Another type of possible accessory muscular pathway was observed in the heart of a newborn infant leading from the bundle of His directly to septal myocardium and by-passing the main bundle branches. Such muscular connections have been previously described in studies of random hearts. They have not been mentioned in the few cases of anomalous atrioventricular excitation in which histologic studies were carried out, and their significance requires further investigation.

The author is greatly indebted to Dr. Wallace M. Yater for valuable advice and criticism.

The microscopic sections were prepared by Miss Mollie L. Hill. The photomicrographs were made by Mr. Roy M. Reeve of the Army Institute of Pathology and by Mr. J. G. Nale-Povic and Mr. Victor R. Landi of the Medical Illustration Laboratory, Veterans Administration Hospital, Washington, D. C.

REFERENCES

1. His, W., Jr.: Die Thaetigkeit des embryonalen Herzens und deren Bedeutung fuer die Lehre von der Herzbewegung beim Erwachsenen, Arb. a. d. med. Klin. zu Leipz. p. 14, 1893.
2. Retzer, R.: Ueber die musculoese Verbindung zwischen Vorhof und Ventrikel des Saeugetierherzens, Arch. f. Anat. u. Physiol., Anat. Abt., p. 1, 1904.
3. Braeunig, K.: Ueber musculoese Verbindungen zwischen Vorkammer und Kammer bei verschiedenen Wirbeltierherzen, Arch. f. Anat. u. Physiol., Physiolog. Abt., Suppl. Band, p. 1, 1904.
4. Tawara, S.: Das Reitzleitungssystem des Saeugetierherzens, Jena, 1906, Gustav Fischer.
5. Keith, A., and Flack, M. W.: The Auriculo-Ventricular Bundle of the Human Heart, Lancet **2**:359, 1906.
6. Keith, A., and Flack, M. W.: The Form and Nature of the Muscular Connections Between the Primary Divisions of the Vertebrate Heart, J. Anat. & Physiol. **41**:172, 1907.
7. Fahr: Zur Frage der atrioventrikulaeren Muskelverbindung in Herzen, Verhandl. d. deutsch. path. Gesellsch. **12**:153, 1908.
8. Moenckeberg, J. G.: Untersuchungen ueber das Atrioventrikularbuendel im menschlichen Herzen, Jena, 1908, Gustav Fischer.
9. Curran, E. J.: A Constant Bursa in Relation With the Bundle of His; With Studies of the Auricular Connections of the Bundle, Anat. Rec. **3**:618, 1909.
10. DeWitt, L. M.: Observations on the Sino-ventricular Connecting System of the Mammalian Heart, Anat. Rec. **3**:475, 1909.
11. De Gaetani, L.: Il fascio atrio-ventricolare nell 'uomo, Anat. Anz. **39**:209, 1911.
12. Robertson, A. W. D.: The Anatomy of the Sino-ventricular Connecting System of the Heart, Australian M. J. **16**:21, 1911.
13. Holl, M.: Makroskopische Darstellung des atrioventrikularen Verbindungsbuendels am menschlichen und tierischen Herzen, Arch. f. Anat. u. Physiol., Anat. Abt., p. 62, 1912.
14. Tandler, J.: Anatomie des Herzens, Jena, 1913, Gustav Fischer.
15. Retzer, R.: The Sino-ventricular Bundle: A Functional Interpretation of Morphological Findings, Carnegie Inst., Contrib. Embryol., Wash. **9**:143, 1920.
16. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, London, 1920, Shaw & Sons, Ltd.
17. Holmes, A. H.: The Auriculo-ventricular Bundle in Mammals, J. Anat. **55**:269, 1921.
18. Pace, D.: Dix années de recherches sur le tissu spécifique du coeur, Arch. d. mal. du coeur **17**:193, 1924.
19. Wamsley, T.: The Heart. *In*: Quain: Elements of Anatomy, ed. 11, New York, 1929, Longmans, Green & Co.
20. Yater, W. M., Osterberg, A. E., and Hefke, H. W.: Chemical Determination of the Glycogen Ratio in the Bundle of His and the Cardiac Muscle in Man and in the Horse, Arch. Int. Med. **45**:760, 1930.
21. Mahaim, I.: Les maladies organiques du faisceau de His-Tawara, Paris, 1931, Masson et Cie.
22. Blair, D. M., and Davies, F.: Observations on the Conducting System of the Heart, J. Anat. **69**:303, 1935.
23. Yater, W. M.: Pathogenesis of Bundle Branch Block, Arch. Int. Med. **62**:1, 1938.
24. Evans, W.: The Bundle of His, M. J. Australia **1**:962, 1938.
25. Davies, F.: The Conducting System of the Vertebrate Heart, Brit. Heart J. **4**:66, 1942.
26. Walls, E. W.: Dissection of the Atrio-ventricular Node and Bundle in the Human Heart, J. Anat. **79**:45, 1945.
27. Lhamon, R. M.: The Sheath of the Sino-ventricular Bundle, Am. J. Anat. **13**:55, 1912.
28. Cohn, A. E.: Demonstration of Ox Hearts Showing Injection of the Conduction System, Proc. New York Path. Soc. **11**:130, 1911.
29. Cohn, A. E.: Observations on Injection Specimens of the Conduction System in Ox Hearts, Heart **4**:225, 1913.
30. Aagaard, O. C., and Hall, H. C.: Ueber Injektionen des "Reitzleitungssystems" und der Lymphgefaesse des Saeugetierherzens, Anat. Hefte **51**:357, 1914.
31. King, M. R.: The Sino-ventricular System as Demonstrated by the Injection Method, Am. J. Anat. **19**:149, 1916.
32. Cardwell, J. C., and Abramson, D. I.: The Atrioventricular Conduction System of the Beef Heart, Am. J. Anat. **49**:167, 1931.
33. Abramson, D. I., and Margolin, M. A.: A Purkinje Conduction Network in the Myocardium of the Mammalian Ventricles, J. Anat. **70**:250, 1936.
34. Glomset, D. J., and Glomset, A. T. A.: A Morphologic Study of the Cardiac Conduction System in Ungulates, Dog, and Man. Part I. The Sinoatrial Node, AM. HEART J. **20**:389, 1940.

35. Glomset, D. J., and Glomset, A. T. A.: A Morphologic Study of the Cardiac Conduction System in Ungulates, Dog, and Man. Part II. The Purkinje System, AM. HEART J. **20**:677, 1940.
36. Glomset, D. J., and Birge, R. F.: A Morphologic Study of the Conduction System. Part IV. The Anatomy of the Upper Part of the Ventricular Septum in Man, AM. HEART J. **29**:526, 1945.
37. Purkinje, J. E.: Mikroskopisch-neurologische Beobachtungen, Arch. f. Anat., Physiol. u. wissensch. Med., p. 281, 1845.
38. Todd, T. W.: The Specialized Systems of the Heart. *In*: Cowdry, E. V.: Special Cytology, vol. II, New York, 1932, Paul B. Hoeber, Inc., p. 1174.
39. Truex, R. C., and Copenhaver, W. M.: Histology of the Moderator Band in Man and Other Mammals With Special Reference to the Conduction System, J. Anat. **80**:173, 1947.
40. Mallory, F. B.: Pathological Technique, Philadelphia, 1944, W. B. Saunders Company, p. 156.
41. Mahaim, I.: Kent's Fibers and the A-V Paraspecific Conduction Through the Upper Connections of the Bundle of His-Tawara, AM. HEART J. **33**:651, 1947.
42. Robb, J. S., and Turman, W. G.: Further Consideration of the QT Interval, Am. J. M. Sc. **214**:180, 1947.
43. Spalteholz, W.: Hand-atlas of Human Anatomy, ed. 7, Philadelphia, 1937, J. B. Lippincott Company, p. 389b.
44. Kent, A. F. S.:
    (a) Researches on the Structure and Function of the Mammalian Heart, J. Physiol. **14**:233, 1893.
    (b) Proc. Physiol. Soc. No. VI, Nov. 12, 1892, J. Physiol. **14**:XXIII, 1893.
    (c) Observations on the Auriculo-ventricular Junction of the Mammalian Heart, Quart. J. Exper. Physiol. **7**:193, 1913.
    (d) Neuro-muscular Structures in the Heart, Proc. Roy. Soc., London, s. B. (Biological Sciences) **87**:198, 1914.
    (e) The Structure of the Cardiac Tissues at the Auriculo-ventricular Junction, Proc. Physiol. Soc., Nov. 15, 1913, J. Physiol. **47**:XVII, 1913.
    (f) The Right Lateral Auriculo-ventricular Junction of the Heart, Proc. Physiol. Soc., Mar. 14, 1914, J. Physiol. **48**:XXII, 1914.
    (g) A Conducting Path Between the Right Auricle and the External Wall of the Right Ventricle in the Heart of the Mammal, Proc. Physiol. Soc., June 27, 1914, J. Physiol. **48**:LVII, 1914.
45. Wood, F. C., Wolferth, C. C., and Geckeler, G. D.: Histologic Demonstration of Accessory Muscular Connections Between Auricle and Ventricle in a Case of Short P-R Interval and Prolonged QRS Complex, AM. HEART J. **25**:454, 1943.
46. Oehnell, R. F.: Pre-excitation, a Cardiac Abnormality, Acta med. Scandinav. Suppl. 152, 1944.
47. Deerhake, H. G., Kimball, J. L., Burch, G. E., and Henthorne, J. C.: Wolff-Parkinson-White Syndrome; Histological Study of the Cardiac Septum and Auriculo-ventricular Groove in One Case. (To be published.) Cited by Kimball, J. L., and Burch, G.: The Prognosis of the Wolff-Parkinson-White Syndrome, Ann. Int. Med. **27**:239, 1947.
48. Wolferth, C. C., and Wood, F. C.: The Mechanism of Production of Short P-R Interval and Prolonged QRS Complexes in Patients With Presumably Undamaged Hearts: Hypothesis of an Accessory Pathway of Auriculo-ventricular Conduction (Bundle of Kent), AM. HEART J. **8**:297, 1933.
49. Wilson, J. G.: The Nerves of the Atrioventricular Bundle, Proc. Roy. Soc., London, s. B. **81**:151, 1909.
50. Meiklejohn, J.: On the Innervation of the Nodal Tissue of the Mammalian Heart, J. Anat. & Physiol. **48**:1, 1913.
51. Bachmann, G.: The Distribution of the Vagus Nerves to the Sino-auricular Junction of the Mammalian Heart, Am. J. Physiol. **63**:300, 1923.
52. Perman, E.: Anatomische Untersuchungen ueber die Herznerven bei den hoeheren Saeugetieren und beim Menschen, Ztschr. f. Anat. u. Entwcklngsgesch. **71**:382, 1924.
53. Fukutake, K.: Beitraege zur Histologie und Entwicklungsgeschichte des Herznervensystems, Ztschr. f. Anat. u. Entwcklngsgesch. **76**:592, 1925.
54. Woollard, H. H.: The Innervation of the Heart, J. Anat. **60**:345, 1926.
55. Jones, T.: Intramuscular Nerve Elements of the Ventricular Muscle, J. Anat. **61**:247, 1927.
56. Schurawlew, A. N.: Die Herznerven des Hundes, Ztschr. f. Anat. u. Entwcklngsgesch. **86**:655, 1928.
57. King, A. B.: Nerve Endings in the Cardiac Muscle of the Rat, Bull. Johns Hopkins Hosp. **65**:489, 1939.
58. Nonidez, J. F.: The Structure and Innervation of the Conductive System of the Heart of the Dog and Rhesus Monkey as Seen With a Silver Impregnation Technique, AM. HEART J. **26**:577, 1943.

EXPERIMENTAL STUDIES ON THE VALIDITY OF THE CENTRAL TERMINAL OF WILSON AS AN INDIFFERENT REFERENCE POINT

M. Dolgin, M.D., S. Grau, M.D., and L. N. Katz, M.D.
Chicago, Ill.

THE central terminal method of Wilson[1] has been the most widely discussed means to free the precordial electrocardiogram from the electrical influence of the "indifferent" electrode when the latter is placed on one of the extremities. Universal acceptance of this method, however, has been withheld because its validity is based, in turn, on the validity of the classical Einthoven equilateral triangle hypothesis.[2] There can be no disagreement with the electrical scheme of Wilson (based on Kirchhoff's law) in so far as it results in a common terminus, the potential of which is equal to the algebraic mean of the potentials of the right arm, left arm, and left leg.[1] However, the central terminal becomes a truly indifferent reference point (zero potential) only when the sum of the potentials of the right arm, left arm, and left leg (the apices of the triangle) is equal to zero.[1] When the assumptions underlying the Einthoven theory are accepted without reservation, it can be shown mathematically that the sum of the potentials of the right arm, left arm, and left leg does equal zero.[3] It has been recognized by Einthoven,[4] as well as his more recent exponents,[5,6] that these assumptions were only "first approximations of the truth."[6] It has been necessary, therefore, to subject both the Einthoven hypothesis and its practical application to experimental analysis in order to determine the magnitude of the error involved in the basic assumptions.

The studies designed to determine the validity of the Wilson central terminal as a truly indifferent reference point may be divided into two main categories: (1) experiments testing the accuracy of the Einthoven equilateral triangle hypothesis, its individual assumptions or the theory as a whole, and (2) experiments determining the potential of the central terminal directly by comparing it with reference points which were considered to be truly indifferent (zero potential) by construction. These studies have been recently reviewed in part by Wilson and his associates[6] and may be interpreted briefly as follows:

1. The original Einthoven assumption that the heart may be considered electrically equivalent to a small dipole has been modified in the sense that a battery analogy would be more in accord with the facts and would avoid oversimplification.[7,8] This modification does not compromise the original theory

From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Ill. The Department is supported in part by the Michael Reese Research Foundation.
Aided by the A. D. Nast Fund for Cardiovascular Research.

since in either case, at any instant, the algebraic sum of the differences in potential existing in the heart can be treated as a vector and projected on the frontal plane of the body. The experiments which have attempted to determine whether or not the body may be considered a homogeneous volume conductor have yielded conflicting results.[9-16] The anatomic assumptions of the Einthoven theory involve an obvious and variable error,[6,17] the magnitude of which has not been directly determined. The results of experiments examining the Einthoven theory as a whole have been more uniform in indicating that a reasonably close agreement exists between the observed facts and the predictions of the theory.[6,18] However, here, too, there is difference of opinion.[19,20]

2. The direct measurements of the potential of the central terminal are of greater and more immediate interest since they determine the error of a method, the theoretical background of which is only approximately sound. The principal of these experiments has been the comparison of the difference in potential between fixed points on the body surface and the Wilson central terminal, on the one hand, and a reference point considered to be truly indifferent by construction, on the other. In addition, measurements have been made of the difference in potential between the Wilson central terminal and the truly indifferent reference point. In three of these experiments,[6,21,22] the subjects were immersed in water (distilled, tap, or lake). Eckey and Fröhlich[21] and Burger[22] used the bounding metal screen as the reference point of zero potential, whereas Wilson[6] placed his indifferent electrode in the lake water eleven feet from the immersed subject. The validity of these experiments in providing truly indifferent reference points has been discussed at length by Wilson[6] and by Wolferth and Livezey[20] and need not be reviewed here except by comment that while these reference points may not necessarily be at zero potential, they are sufficiently indifferent, especially when the reference electrode is placed at a relatively great distance from the heart. Viana[23] studied this problem by constructing a large equilateral triangle and placing the subject in the center. The triangle and subject (rabbit and man) were placed on moist ground and wires were led to a common terminus from three electrodes imbedded in the ground at the apices of the triangle. This terminus was used as the indifferent reference point. The results of these experiments have shown, with one exception, that: (1) The difference in potential between fixed points on the body surface and the indifferent reference point was greater than the difference in potential between the Wilson central terminal and the indifferent reference point. (2) The potential of the Wilson central terminal (when paired to the indifferent reference point) was not consistently zero, but ranged from 0.15 to 0.36 millivolt. In the single experiment which Wilson performed,[6] the difference in potential between the left leg and the indifferent reference point in the lake was less than the difference in potential between the central terminal and the distant reference point. This indicated that in this subject the left leg was more indifferent than the Wilson central terminal. This may have been a rare phenomenon as was suggested,[6] but if it were to occur sufficiently frequently, it would obviously destroy the purported advantage of the central terminal over the extremities as the ideal location for the distant electrode. The observation of Wilson has prompted us to re-

examine experimentally the validity of the central terminal as a null reference point. The experiments to be described are modifications of the immersion studies which have been referred to.[6,21,22]

MATERIAL AND METHOD (Illustrated in Fig. 1)

Normal adult men were placed in a tile-lined indoor swimming pool, 75 feet by 24 feet, containing chlorinated tap water (0.86 parts per million). The subjects were upright and immersed to such a depth that the water level reached to, and included the chin or lips. The subjects could be so positioned that they were approximately equidistant from the two ends and from the two sides of the pool. An equilateral triangle, each side of which was ten feet long, was built of three narrow planks of light wood. A ten-foot length of No. 18 braided copper wire, insulated except at its ends, was fixed with adhesive tape at each apex of the wooden triangle so that eighteen inches of wire were suspended directly into the water below its surface. To the tip of each of the immersed wires was attached a German silver electrode measuring 2 inches by 1.5 inches (*E*). These three submerged electrodes formed the apices of a horizontal equilateral triangle (*EEE*) eighteen inches below the surface of the water, each side of which was ten feet long and the plane of which passed approximately through the apex of the heart. The free ends of the three wires were joined and inserted into one post of a double binding post electrode (CT_E). The other binding post of CT_E was used whenever this external central terminal was connected to the electrocardiograph. The terminal CT_E was taped in place on a small block of wood encased in rubber sheeting which, in turn, was fixed in place on one of the sides of the wooden triangle. This arrangement prevented immersion of the terminal. The wooden triangle was floated into position so that its apices were equidistant from the centrally placed subject and anchored with lengths of thin cord to fixed objects on the sides of the pool. Each apex of the triangle was approximately seven feet from the nearest side of the pool. Throughout the experiments the central position of the subject was checked closely.

A plank of wood approximately one foot wide and eight feet long was arranged at one side of the pool in the form of a diving board which extended out to and faced the subject. The segment which rested on the side of the pool was held in place with the electrocardiograph (*ECG*). To the end of the segment extending over the water was fixed a specially constructed junction box (*JB*) to which was connected the patient lead wire cable (*PLW*). A chest lead wire (*CLW*) fifteen feet long was inserted into a separate binding post on the junction box.* When properly connected, this long chest lead wire substituted for the ordinary chest lead wire on the patient lead wire cable and could also be used (IP_E) to connect a distant point E' (consisting of a German silver electrode like those forming the equilateral triangle, *EEE* in the pool) with the electrocardiograph. A long wire also attached to the junction box was suspended on the surface of the water ten to thirteen feet from the subject and served as a ground wire (*GW*), being

*We are indebted to Dr. A. Miller of the Sanborn Co., Cambridge, Mass., for his advice on the construction of the special equipment used in these experiments.

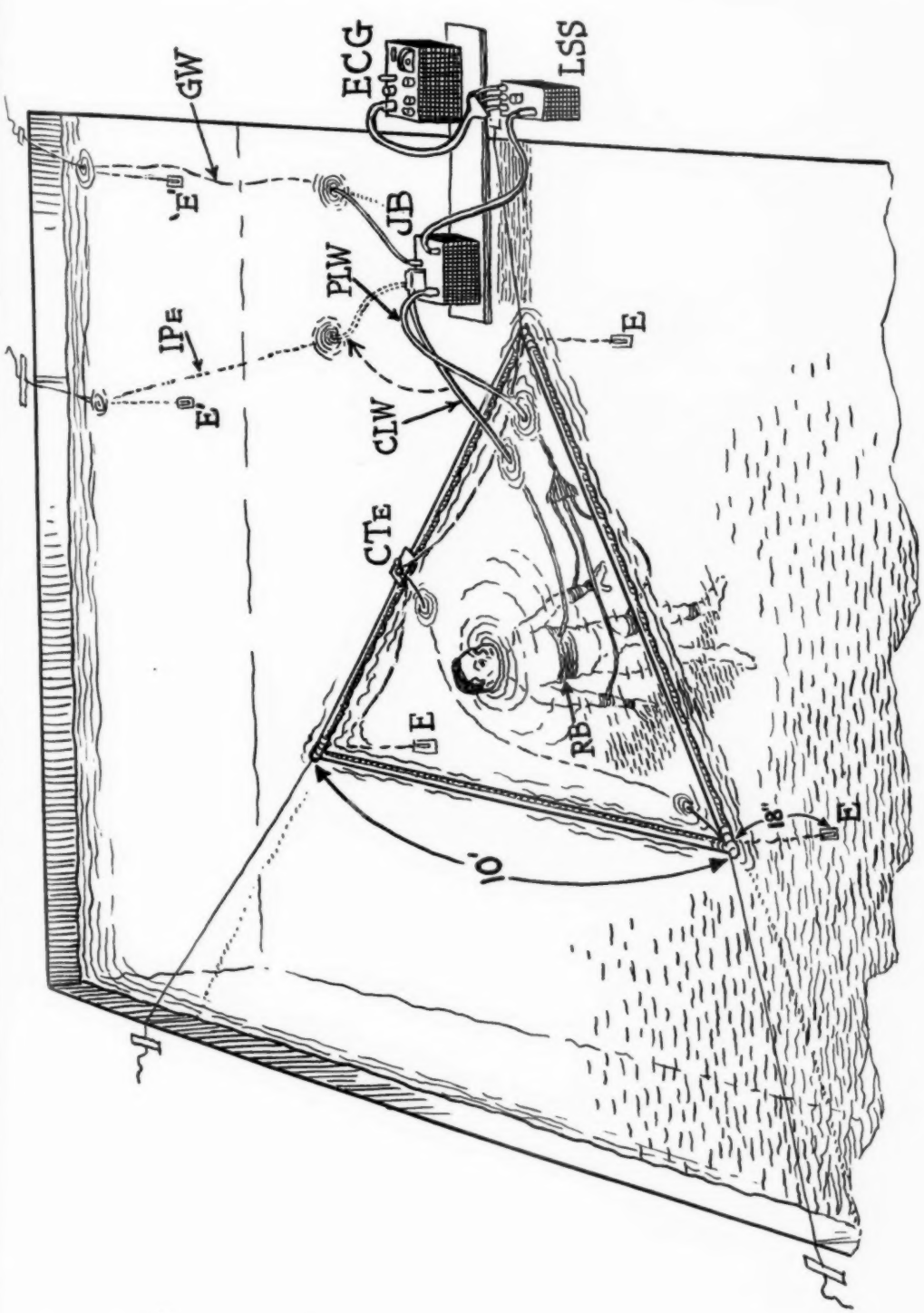


Fig. 1.—A diagrammatic representation of the arrangements and equipment used in the experiments. Discussed in text.

connected to a ground electrode *'E'*. The junction box was connected by an extension cable to a standard lead selector switch box (*LSS*) on the side of the pool; this switch was connected, in turn, to a vacuum tube amplifier type of electrocardiograph (Sanborn) in the usual manner. A switch on the instrument panel of the electrocardiograph facilitated reversal of polarity without the need for changing the actual wire connections in the machine. Two electrodes each were placed on the right arm, left arm, and left leg of the subject. A perforated rubber belt (*RB*) was placed around the chest of the subject allowing two chest electrodes to remain fixed in place without manual aid. One electrode was located in the fourth intercostal space just to the left of the sternum (which we labelled C_a) and the other was located in the left anterior axillary line at the same horizontal level as the first chest electrode (labelled C_b). Once immersed, the subject accomplished all changes in the location of the lead wires without assistance. Electrocardiographic records were also obtained when the subjects were on land at the usual standardization (1 mv. equals 1 cm. deflection). Records with the subjects immersed in the pool were taken at the maximum sensitivity of the machine (1 mv. equals 2 cm. deflection).

The following leads were recorded in each experiment and are so labelled in Figs. 2 to 4:

I. Before immersion; labelled *L* for land, (subject standing)
   - A. Standard limb leads I, II, III
   - B. Extremity leads
     1. Right arm (RA) minus Wilson central terminal (CT_W)
     2. Left arm (LA) minus CT_W
     3. Left leg (LL) minus CT_W*
   - C. Precordial leads
     1. Chest electrode at fourth left parasternal intercostal space (C_a)
        - a. C_a minus RA
        - b. C_a minus LA
        - c. C_a minus LL
        - d. C_a minus CT_W†
     2. Chest electrode at left anterior axillary line (C_b)
        - a. C_b minus RA
        - b. C_b minus LA
        - c. C_b minus LL
        - d. C_b minus CT_W†

II. During immersion; labelled *W* for water, (subject standing):
   - A. Standard limb leads I, II, III
   - B. Extremity leads
     1. RA minus CT_W
     2. LA minus CT_W

*I, B 1, 2, and 3 are, respectively, V_R, V_L, and V_F.
†I, C 1 a, b, c, and d and I, C 2 a, b, c, and d are, respectively, C_R, C_L, C_F, and V leads.

3. LL minus CT_W
4. RA minus constructed external central terminal (CT_E)
5. LA minus CT_E
6. LL minus CT_E

C. Precordial leads

1. Chest electrode at Position C_a
   a. C_a minus RA
   b. C_a minus LA
   c. C_a minus LL
   d. C_a minus CT_W
   e. C_a minus CT_E
2. Chest electrode at Position C_b
   a. C_b minus RA
   b. C_b minus LA
   c. C_b minus LL
   d. C_b minus CT_W
   e. C_b minus CT_E

D. CT_W minus CT_E

In four experiments the long chest lead wire was fixed in place in the water thirteen to fourteen feet from the subject, connected with a submerged electrode, and was then considered as an external indifferent reference point (IP_E). The water depth at Point IP_E was three to four feet and the electrode was suspended one foot below the surface. In these four experiments the following additional leads were taken with the subject still immersed:

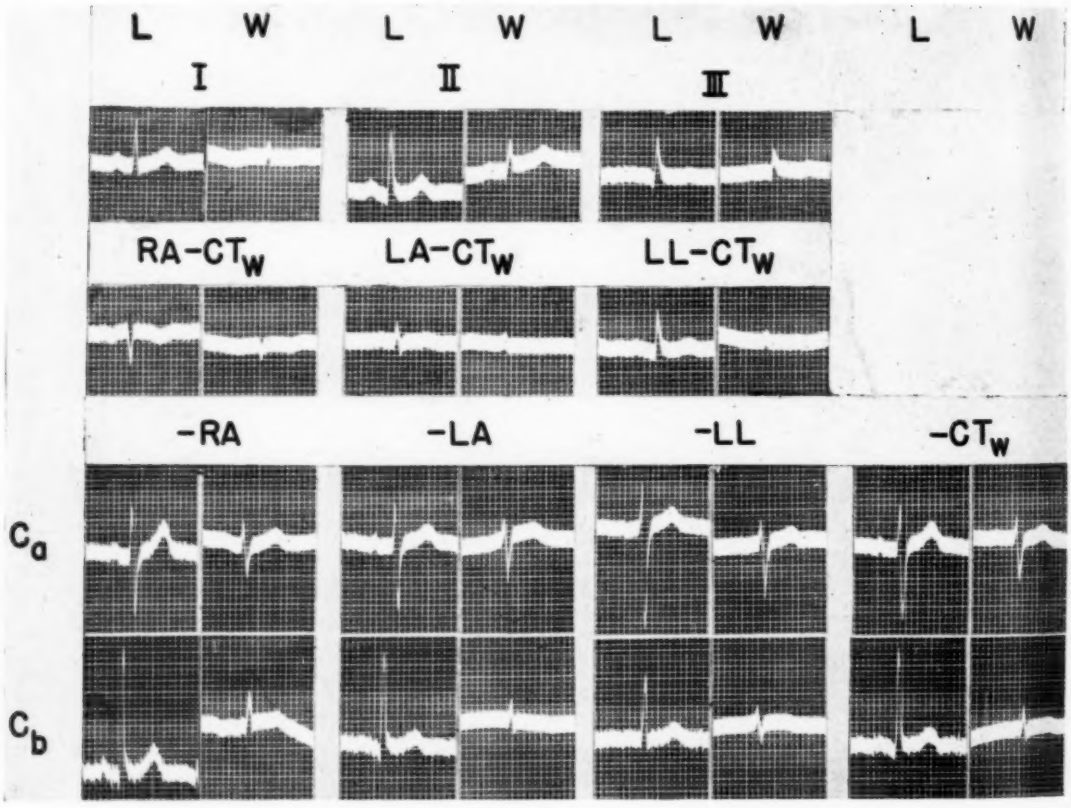
1. RA minus IP_E
2. LA minus IP_E
3. LL minus IP_E
4. C_a minus IP_E
5. C_b minus IP_E
6. CT_W minus IP_E

RESULTS

Nine experiments were performed. It was necessary to discard two of these because of somatic tremors, alternating current, and other artefacts. The results presented are based on the remaining seven experiments. The short circuiting effect of the water caused marked reduction of the amplitude of the deflections so that even with double standardization the deflections in water were about 20 to 30 per cent of their size on land. A complete experiment is reproduced in Fig. 2. The marked shunting effect encountered in water is exemplified in Fig. 2,*A*.

The results may be summarized under five headings:

1. The difference in potential between any of the three extremities and either the external central terminal or the external indifferent reference point in the water was greater in all experiments than the difference in potential between the Wilson central terminal and either of these reference points (Fig. 2,*B*). Hence, on the basis of these experiments, the potential of the Wilson



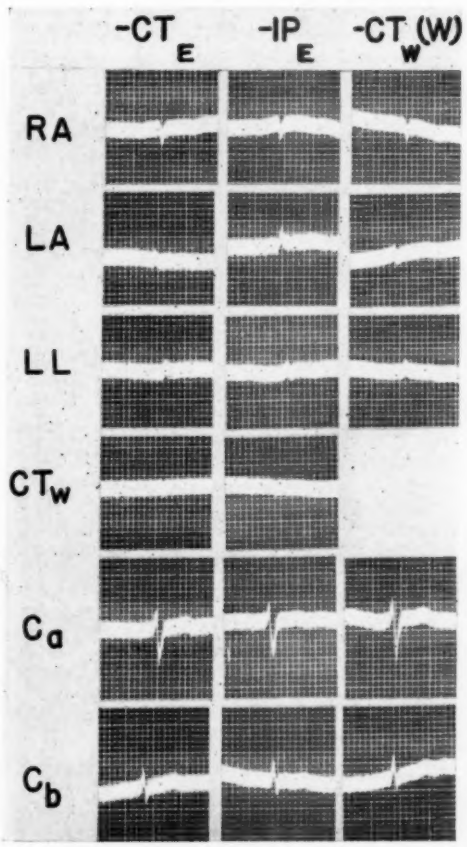
A.

Fig. 2.—An example of a complete experiment. The symbols used are explained in the text.

A, The vertical columns *L* and *W* indicate the records taken, respectively, on land and water. Each lead is identified by symbols at the top of the segments of the record. However, in the case of the chest leads, the chest position is indicated at the left of the row of strips and the reference point at the top of the vertical column. In spite of a standardization of 1 mv. = 2 cm. when the subject was immersed, the amplitude of the deflections is much smaller than before immersion with a standardization of 1 mv. = 1 cm.

B, The lead connection of each lead shown is identified by the lettering at the left of each horizontal row and the heading of each vertical column. The difference in potential between each extremity and either external reference point is greater than the difference in potential between the respective external reference point and the Wilson central terminal. In this case, Lead $LA - CT_E$ resembles $CT_W - CT_E$ more closely than $RA - CT_E$ and $LL - CT_E$. This figure also illustrates the deflections obtained when each of the two chest positions (C_a and C_b) was paired, in turn, with CT_E, IP_E, CT_W. These three reference points gave practically identical records. (*W*) in the third vertical column indicates that the records in this column were taken when the subject was immersed. Discussed in text.

central terminal must be considered more nearly like that of the null reference points than that of any extremity. Similarly, the Wilson central terminal must be considered more indifferent than the right arm, left arm, or left leg. In no instance did we observe a smaller potential difference between any extremity and the external central terminal than between this central terminal and the Wilson central terminal. The same results were obtained when IP_E was used as the indifferent reference point.

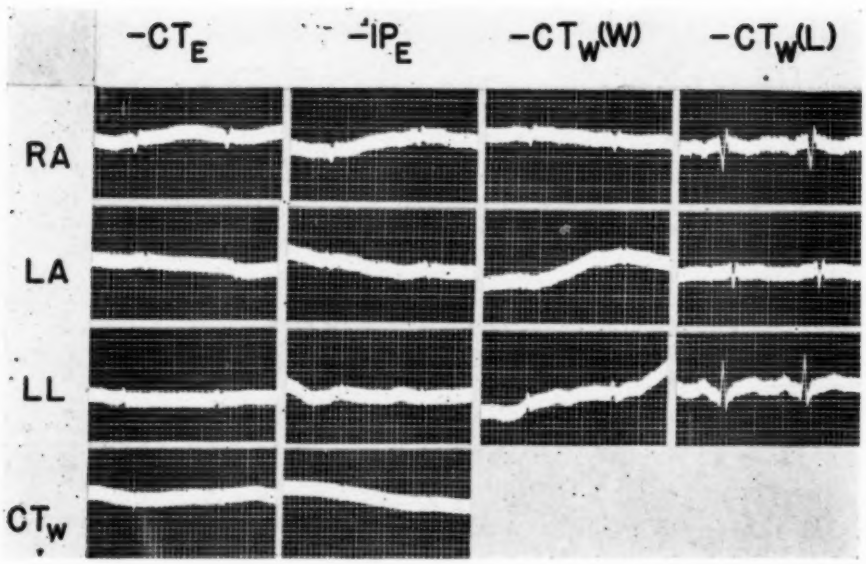


B.

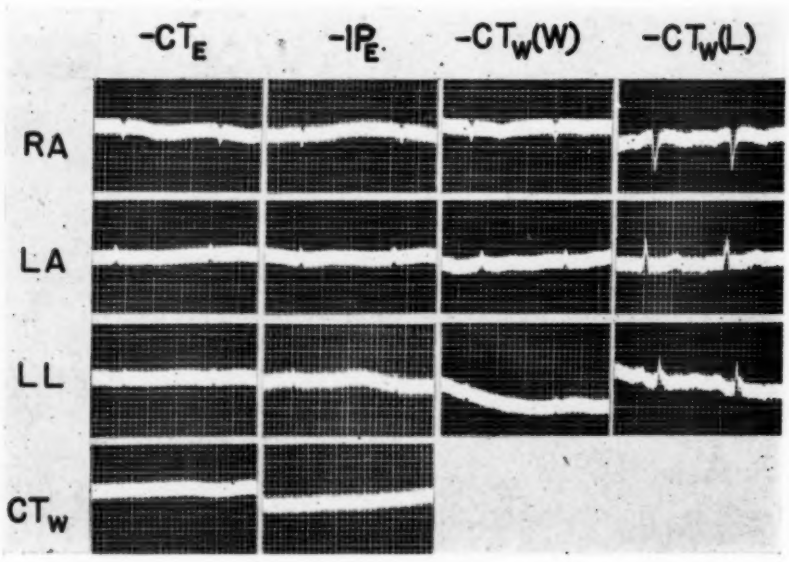
Fig. 2. (Cont'd).—*See opposite page for legend.*

2. In two experiments there was no recorded difference in potential between the Wilson central terminal and the external central terminal (Fig. 4,*A*). In the remainder there was a small difference of potential, the Wilson central terminal being slightly negative in relation to the external central terminal in all but one experiment (Figs. 2,*B* and 4,*B* and *C*).

3. In the electrocardiograms which showed small deflections when the left arm was paired with the external central terminal and relatively tall upright



A.



B.

Fig. 3.—Two additional examples of the potential difference obtained when each of the three extremities was paired, in turn, with CT_E, IP_E, and CT_W. The symbols used are explained in the text. (*W*) and (*L*) in the third and fourth vertical columns represent, respectively, the extremity leads taken in water and on land. The latter records are shown for comparison with the former.

***A*, The Wilson central terminal is slightly negative to each external reference point. The difference in potential between *LA* and CT_W or either external reference point resembles the potential difference between CT_W and either external reference point more closely than does the difference in potential between *RA* or *LL* and these points.**

***B*, The Wilson central terminal is at the same potential as each of the external reference points. The potentials of *LA* and *LL* are approximately the same and more like that of CT_W than *RA*. (*W*) means subject immersed; (*L*), subject on land. Discussed in text.**

deflections when the left leg was paired with the external central terminal, LA—CT_E more closely resembled, but was not identical to, the potential difference between the Wilson central terminal and the external central terminal than did either of the other extremity leads, RA—CT_E and LL—CT_E, (Fig. 3,*A*). In the electrocardiograms which showed small upright deflections in both LA—CT_E and LL—CT_E, either LL—CT_E or both LL—CT_E and LA—CT_E resembled CT_W—CT_E (Fig. 3,*B*). Similar results were obtained when IP_E was used as the indifferent point. Hence, as would be expected, the potentials of the extremities vary with the direction of spread of the impulse in the heart and the position of the heart in the thorax, and, depending on this position, the left arm or left leg may, at times, have potentials which are almost as small as those of the Wilson central terminal.

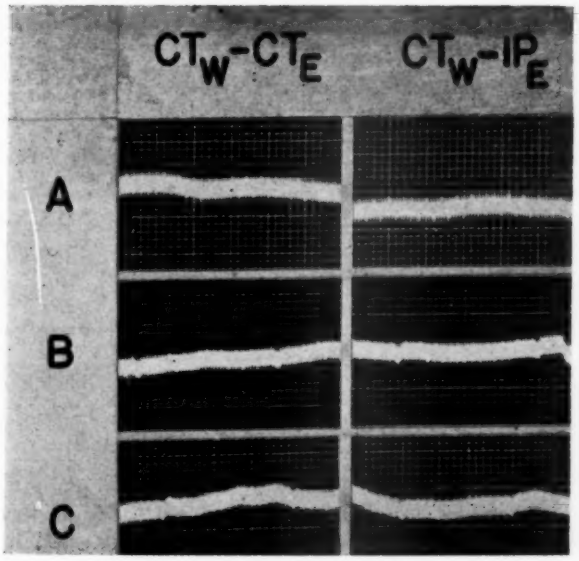


Fig. 4.—Three experiments in which the Wilson central terminal was paired, in turn, to the external central terminal (*CTE*) and the distant reference point (*IPE*). In *A*, the two external reference points have the same potential as the Wilson central terminal. In *B* and *C*, the two external reference points have potentials different from each other and from that of the Wilson central terminal. Discussed in test.

4. The deflections obtained by pairing each of the two fixed points on the chest with either the external central terminal (CT_E) or with the indifferent point in the water (IP_E) were identical to those obtained when these fixed points were paired with the Wilson central terminal. Similar results were also observed when the extremity leads were taken in the same manner. When slight differences existed they could be explained on the basis of the small potential of the Wilson terminal (Fig. 2,*B*). Precordial positions were selected in order to obtain larger deflections.

5. In four experiments it was possible to compare the potentials of the two indifferent points (CT_E and IP_E) by pairing each with CT_W. In one experiment

both the external central terminal and the distant point in the water were at the same potential as the Wilson central terminal (Fig. 4,*A*). In three experiments a small difference was observed between $CT_W - CT_E$ and $CT_W - IP_E$, indicating that the two indifferent points were not constantly at the same potential (Fig. 4,*B* and *C*). Nevertheless, regardless of the type of reference point used (CT_E or IP_E), the potential of the Wilson central terminal was always more nearly like that of the reference point than the potential of any extremity (Fig. 2,*B*).

COMMENT

The principal limitation to the quantitative analysis of our data was the small size of the deflections resulting from the short circuiting effect of the water. It was felt that actual measurements of these small deflections would involve an error probably sufficiently large to invalidate the measurements themselves. Consequently, no quantitative data are given and no specific values are assigned to the potential variations of the Wilson central terminal when it was paired to external reference points. Nevertheless, qualitatively, the electrocardiograms can be interpreted without difficulty. The opinions of several independent observers who inspected the records were identical. We feel, therefore, that the results given are justified, especially since they represent some departure from previous views of the department from which this study comes.

As to the validity of the conclusion that the Wilson central terminal in these experiments was consistently more indifferent than any of the fixed points on the body surface, it is necessary to comment on the external central terminal (CT_E) which we used as the ultimate null reference point. It is apparent that our equilateral triangle was constructed in the horizontal plane of the body, whereas strict electrophysical theory would demand that the triangle lie in the same plane as the vector which expresses the heart's mean electromotive force. This plane forms an angle with the horizontal as well as the frontal planes of the body. Nor can we assume any strictly constant relationship between these two planes in view of the differences in position of the heart from subject to subject. Furthermore, the plane of our equilateral triangle did not divide the conducting medium (water) into two identical parts any more than does the Einthoven triangle in the frontal plane divide the body into two equal parts. However, as Wilson has pointed out,[6] the magnitude of the errors involved in these spatial arrangements decreases as the distance of the apices of the triangle from the heart increases. It is on the basis of the great distance of these apices from the heart that we, and presumably Viana,[23] considered the central terminal formed from the large external equilateral triangle as a valid indifferent reference point. We do not claim that the potential of our external central terminal is necessarily zero, but only that it is smaller than the potential of points on the body surface. The fact that similar results were obtained when our reference point was at a great distance from the heart, and not dependent on the position of the plane of the triangle, fortifies this view.

The results of our experiments confirm the work of previous investigators. It may be concluded, therefore, that the Wilson central terminal, while not con-

stantly at zero potential, is consistently more indifferent from subject to subject than any fixed point on the body surface. It follows that the errors inherent in the assumptions of the Einthoven equilateral triangle hypothesis are not sufficiently large to invalidate completely the theory on which this central terminal is based nor to interfere with the usefulness of the central terminal in clinical electrocardiography. It was previously noted that in some subjects the spread of the impulse through the heart and the position of the heart may cause either the left leg or the left arm to be almost as indifferent as the central terminal. Therefore, in such subjects a precordial lead obtained by placing the distant electrode on the left leg or left arm will be practically the same as the V (central terminal) lead. The advantage of the central terminal as a reference point lies in the fact that it is not dependent on any particular position of the heart, but rather that it remains more indifferent in a series of subjects than the extremities, irrespective of these variables.

SUMMARY AND CONCLUSIONS

1. The validity of the central terminal as a truly indifferent reference point has been re-evaluated in a series of immersion experiments. The potential of this central terminal was compared to two other reference points, considered to be indifferent by construction. The first was an external central terminal formed from a large submerged equilateral triangle, the apices of which were equidistant from the immersed subject. The second was a distant point under water thirteen to fourteen feet from the immersed subject.

2. The difference in potential between either of these reference points and the Wilson central terminal was consistently smaller from subject to subject than the difference in potential between each of five fixed points on the body surface and either external reference point or the Wilson central terminal. The five fixed points were the right arm, left arm, left leg, and two points on the anterior chest wall. The deflections obtained by pairing each of the five points with either external reference point were identical to or closely resembled the deflections obtained by pairing these points with the Wilson central terminal.

3. In two of seven experiments the Wilson central terminal and the external central terminal were at the same potential throughout the cardiac cycle. In the remainder, the Wilson central terminal was slightly negative (four experiments) or positive (one experiment) to the external central terminal. In one of four experiments the two external reference points were at the same potential, whereas in the remainder there was a slight difference.

4. The results confirm the experience of others and indicate that the Wilson central terminal may be considered a more uniformly indifferent reference point than any of the extremities.

We are indebted to the various house officers who submitted patiently as subjects for this study.

REFERENCES

1. Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Electrocardiograms That Represent the Potential Variations of a Single Electrode, Am. Heart J. 9:447, 1934.

2. Einthoven, W., Fahr, G., and de Waart, A.: Ueber die Richtung und die manifeste Grösse dei Potentalschwankungen im menschlichen Herzen und ueber den Einfluss der Herzlage auf die Form des Elektrokardiogramms, Arch. f. d. ges. Physiol. **150**:275, 1913.
3. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Potential Variations Produced by the Heart Beat at the Apices of Einthoven's Triangle, Am. Heart J. **7**:207, 1931.
4. Cited by Wilson.[6]
5. Wilson, F. N.: The Distribution of the Potential Differences Produced by the Heart Beat Within the Body and at Its Surface, Am. Heart J. **5**:599, 1930.
6. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., and Barker, P. S.: On Einthoven's Triangle, the Theory of Unipolar Electrocardiographic Leads, and the Interpretation of the Precordial Electrocardiogram, Am. Heart J. **32**:277, 1946.
7. Katz, L. N.: Genesis of the Electrocardiogram, Physiol. Rev. **27**:398, 1947.
8. Goldberger, E.: Unipolar Lead Electrocardiography, Philadelphia, 1947, Lea & Febiger.
9. Eyster, J. A. E., Maresh, F., and Krasno, M. R.: The Nature of the Electrical Field Around the Heart, Am. J. Physiol. **106**:574, 1933.
10. Katz, L. N., and Korey, H.: The Manner in Which the Electric Currents Generated by the Heart Are Conducted Away, Am. J. Physiol. **111**:83, 1935.
11. Katz, L. N., Gutman, I., and Ocko, F. H.: Alteration in the Electrical Field Produced by the Changes in the Contacts of the Heart With the Body, Am. J. Physiol. **116**:302, 1936.
12. Katz, L. N., Sigman, E., Gutman, I., and Ocko, F. H.: The Effect of Good Electrical Conductors Introduced Near the Heart on the Electrocardiogram, Am. J. Physiol. **116**:343, 1936.
13. Lindner, E., and Katz, L. N.: The Relative Conductivity of the Tissues in Contact With the Heart. Observations on Animals With Closed Chests, Am. J. Physiol. **125**:625, 1939.
14. Benjamin, J. E., Landt, H., and Culver, L. R.: The Body as a Volume Conductor and Its Influence on the Electrical Field of the Heart, Am. J. M. Sc. **195**:759, 1938.
15. Kaufman, W., and Johnston, F. D.: The Electrical Conductivity of the Tissues Near the Heart and Its Bearing on the Distribution of the Cardiac Action Currents, Am. Heart J. **26**:42, 1943.
16. Burger, H. C., and van Milaan, J. B.: Heart—Vector and Leads. Part II, Brit. Heart J. **9**:154, 1947.
17. Katz, L. N., Electrocardiography, ed. 2, Philadelphia, 1946, Lea & Febiger.
18. Goldberger, E.: The Validity of the Einthoven Triangle Hypothesis, Am. Heart J. **29**:369, 1945.
19. Wolferth, C. C., Livezey, M. M., and Wood, F. C.: The Relationships of Leads I, Chest Leads From the C_3, C_4 and C_5 Positions, and Certain Leads Made From Each Shoulder Region: The Bearing of These Observations Upon the Einthoven Equilateral Triangle Hypothesis and Upon the Formation of Lead I, Am. Heart J. **21**:215, 1941.
20. Wolferth, C. C., and Livezey, M. M.: A Study of Methods of Making So-called Unipolar Electrocardiograms, Am. Heart J. **27**:764, 1944.
21. Eckey, P., and Fröhlich, R.: Zur Frage der Unipolaren Ableitung des Elektrokardiogramms, Arch. f. Kreislaufforsch. **2**:349, 1938.
22. Burger, R.: Ueber das elecktrische Feld des Herzens, Cardiologia **3**:56, 1939.
23. Viana, F. P.: Determinācao Experimental do Potencial do Terminal Central de Wilson, Amatus, **5**:133, 1946.

POTASSIUM AUTOINTOXICATION FROM HEMOLYSIS OF RED CELLS

J. WENER, M.D., H. STANSFIELD, M.D., H. E. HOFF, M.D., AND H. A. WINTER, B.Sc.

MONTREAL, CANADA

IT IS generally known that in man and in certain species of animals there is a marked difference between the concentration of potassium in the plasma and that normally present in the erythrocytes.[1] In the latter, the amount of potassium is approximately twenty times greater than that found in the plasma. In recent years, there has been an increasing number of reports dealing with the syndrome of potassium intoxication, especially concerning the effects of high potassium on cardiac musculature. The present study was undertaken to determine if the sudden liberation of the intracellular potassium in conditions marked by rapid and extensive intravascular hemolysis of erythrocytes would be sufficient to cause or bring on the signs and symptoms of potassium intoxication.

Ringer[2] showed that excess of potassium caused the frog's heart to stop in diastole. In 1938, Winkler, Hoff, and Smith[3] produced potassium intoxication in dogs by the intravenous injection of isotonic potassium chloride and demonstrated a regular sequence of electrocardiographic changes characteristic of the various stages of this intoxication by which the syndrome could be recognized. These consisted, in succession, of progressive elevation of the T wave, which often becomes diphasic (serum potassium of 5.0 to 7.0 meq. per liter), depression of the S-T segment (8.0 to 10 meq. per liter), disappearance of the P wave (9.0 to 11.0 meq. per liter), widening of the QRS complex, indicating intraventricular block (10.0 to 12 meq. per liter), terminal disorganization of the entire QRS complex, and cardiac arrest (14.0 to 16.0 meq. per liter). In 1941, the same authors[4] noted that dogs made anuric by various means died of typical potassium intoxication, as shown by electrocardiographic and blood potassium studies. Since that time, various authors have reported the occurrence of a similar syndrome in man in uremia[5,7,8,10] and in crush syndrome.[9] The possibility of potassium intoxication due to hemolytic reactions has been suggested by Finch, Sawyer and Flynn.[8] Recently it was shown by Roos, Weisiger, and Moritz[11] that when pigs were severely and extensively scalded, lethal levels of potassium and electrocardiographic changes characteristic of this intoxication were obtained, mainly as the result of the destruction of the red cells.

This work was supported by a grant from the National Research Council of Canada.

From the Department of Physiology, McGill University, Montreal.

In the rabbit the serum potassium is approximately 4.0 meq. per liter, while the erythrocytes contain 106 meq. per liter. If the packed cell volume be taken at 40 per cent, it can be calculated that in the absence of diffusion out of the blood vessels, approximately 15 per cent of the red blood cells must be hemolyzed to raise the serum potassium from 4.0 to 15.0 meq. per liter. If, however, one assumes complete equilibrium between the intravascular and the extracellular fluid, it would require approximately 60 to 65 per cent hemolysis to produce the same elevation of serum potassium. Apparently, therefore, the level of the serum potassium reached will depend on the degree and rate of hemolysis, the extent of diffusion of the excess potassium into the extracellular fluid, and the ability of the kidneys to excrete it.

METHODS

Rabbits were employed because their serum and erythrocyte content of potassium are very similar to that found in man. They were anesthetized with Nembutal and in most of the experiments the constant administration of intratracheal oxygen was employed to maintain oxygen tension in the lungs in case of respiratory arrest. Electrocardiograms were recorded at frequent intervals from Lead II. Blood samples for potassium determinations were obtained by direct heart puncture at irregular intervals and at the time of death in most instances. The serum potassium was determined on ashed samples by the colorimetric method of precipitation of silver cobalti-nitrite in ethyl alcohol, and color development in ammonium thiocyanate.[17]

Several methods were used to lake red cells and release their content of potassium. (A) To produce intravascular hemolysis, a 1.0 per cent solution of saponin (Eastman Kodak) was injected intravenously into the femoral veins of twelve rabbits. The amount of saponin injected and the duration of the injection are indicated in Table I. Injection was discontinued when electrocardiograms began to show the final disintegration of the QRS complexes. Blood samples obtained were centrifuged immediately. In Experiments 3, 4, 5, 7, 19, and 21 (Table I) the withdrawn blood samples were placed immediately in graduated uniform bore "Fisher" tubes and packed cell volumes were determined after the blood was centrifuged at 3,000 revolutions per minute for fifteen minutes. No anticoagulants having been used, the packed cell volumes were determined on partially clotted blood. As a control study, the packed cell volume of normal rabbit's clotted blood was compared with that of citrated blood. (B) In an attempt to reproduce an incompatible transfusion reaction, fresh human citrated blood (Group O) was injected intravenously into one rabbit at the rate of 1.0 to 1.5 c.c. per minute until death occurred (Experiment 8, Table II). Human citrated blood (Group O) was hemolyzed completely by freezing and thawing and the laked mixture of blood was injected intravenously into two rabbits at slightly different rates until death occurred (Table II, Experiments 9 and 10). Packed cell volumes of the samples of heart's blood, withdrawn terminally, were determined in Experiments 8 and 10 by the same procedure described in (A). (C) Rabbit blood obtained from donor animals by complete exsanguination

TABLE I. EFFECTS OF INTRAVENOUS INJECTION OF 1 PER CENT SAPONIN

EXP. NO.	WT. (KG.)	AMOUNT INJECTED (C.C.)	DURATION OF INJECTION (MIN.)	TIME OF DEATH AFTER START OF INJECTION (MIN.)	CONC. OF POTASSIUM IN SERUM			DEGREE OF HEMOLYSIS		CHANGES IN ELECTROCARDIOGRAM			
					TIME SAMPLE TAKEN AFTER INJECTION (MIN.)	SAPONIN INJECTED (C.C.)	POTASSIUM CONC. (MEQ./1.)	PACKED CELL VOLUME (PER CENT)	HEMOLYSIS (CALCULATED) (PER CENT)	T-WAVE ELEVATION	RS-T DEPRESSION	LOSS OF P WAVE	SPLIT OF QRS
2	2.9	39.0	27	27	13	19.5	16.9	——	——	+	+	+	+
					27	39.0	16.5	——	——	+	+	+	+
3	4.7	33.5	55	60	30	31.5	7.6	23.0	42.5	+	+	−	−
					46	31.5	7.1	——	——	+	+	−	−
					60	33.5	8.5	24.0	40.0	+	+	+	−
4	3.6	20.0	10	30	19	20.0	17.5	14.0	65.0	+	+	+	+
5	3.6	14.5	6	12	12	14.5	15.0	35.0	12.5	+	+	+	+
6	2.4	13.8	36	36	——	——	——	——	——	+	+	+	+
7	3.3	30.0	8	20	20	30.0	14.5	14.0	65.0	+	+	+	±
13	4.1	32.0	17	45	12	30.0	12.5	——	——	+	+	+	−
					20	32.0	13.5	——	——	+	+	+	±
17	4.1	54.0	30	39	29	52.0	5.2	——	——	+	+	−	−
					39	54.0	8.9	——	——	+	+	±	−
18	3.0	29.0	4	4	4	29.0	13.3	——	——	+	+	±	−
19	3.7	30.0	35	65	65	35.0	14.9	25.0	37.5	+	+	+	+
20	4.1	27.0	20	20	——	——	——	——	——	+	+	+	±
21	3.7	43.0	31	31	6	10.0	11.7	28.0	30.0	+	+	+	−
					16	27.0	14.2	28.0	30.0	+	+	+	±
					21	32.0	20.0	26.5	33.5	+	+	+	+

TABLE II. EFFECTS OF INTRAVENOUS INJECTION OF HUMAN FRESH BLOOD AND HUMAN LAKED BLOOD

EXP. NO.	WEIGHT (KG.)	SOLUTION INJECTED	AMOUNT INJECTED (C.C.)	DURATION OF INJECTION (MIN.)	RATE OF INJECTION (C.C./MIN.)	TIME OF DEATH AFTER INJECTION (MIN.)	DEGREE OF HEMOLYSIS		CONC. OF POTASSIUM IN SERUM		CHANGES IN ELECTROCARDIOGRAM			
							PACKED CELL VOLUME (PER CENT)	HEMOLYSIS (CALCULATED) (PER CENT)	TIME SAMPLE TAKEN AFTER INJECTION (MIN.)	POTASSIUM CONC. (MEQ./1.)	ELEVATION OF T WAVE	RS-T DEPRESSION	LOSS OF P WAVE	SPLIT OF QRS
8	2.3	Citrated human blood (0)	17	19	1–1.5	19	0	100	19	38.2	+	+	+	+
9	3.2	Laked human red cells	31	15	2–4	15	—	—	—	—	+	+	+	+
10	3.1	Laked human red cells	28	24	1.5–2.5	24	15	62.5	24	18.8	+	+	+	+

TABLE III. EFFECTS OF INTRAVENOUS INJECTION OF RABBITS' LAKED RED CELLS

EXP. NO.	WEIGHT (KG.)	SOLUTION INJECTED	AMOUNT INJECTED (C.C.)	DURATION OF INJECTION (MIN.)	RATE OF INJECTION (C.C./MIN.)	TIME OF DEATH AFTER INJECTION (MIN.)	DEGREE OF HEMOLYSIS		CONC. OF POTASSIUM IN SERUM		CHANGES IN ELECTROCARDIOGRAM			
							PACKED CELL VOLUME (PER CENT)	HEMOLYSIS (CALCULATED) (PER CENT)	TIME SAMPLE TAKEN AFTER INJECTION (MIN.)	POTASSIUM CONC. (MEQ./1.)	ELEVATION OF T WAVE	RS-T DEPRESSION	LOSS OF P WAVE	SPLIT OF QRS
22	4.7	Laked rabbit cells	90	35	2–3	35	—	—	14	12.4	+	+	+	∓
									30	19.9	+	+	+	+
									35	20.9	+	+	+	+
23	4.4	Laked rabbit cells	95	20	4–5	20	35	12.5	20	26.7	+	+	+	+

(cannula in the carotid artery) was defibrinated and then centrifuged for twenty minutes at 1,000 revolutions per minute. The supernatant serum was discarded and the remaining red cells were resuspended in isotonic saline. This suspension of red cells was then completely hemolyzed by freezing and thawing. The amount of potassium in the laked red cell suspension was then determined. This solution was then injected intravenously at the rate of 2.0 to 3.0 c.c. and 4.0 to 5.0 c.c. per minute into Rabbits 22 and 23, respectively, until the animals died (Table III, Experiments 22 and 23). Packed cell volume was determined in Experiment 23 by the method described.

To rule out the possible effects of anoxia produced by the extensive destruction of the red cells, electrocardiograms (Lead II) and serum potassium studies were performed on rabbits made anoxic, (1) by overdose with Nembutal (one rabbit), (2) by clamping of the trachea (one rabbit), and (3) by complete exsanguination of the donor rabbits when obtaining blood for the experiments described in (C).

To determine the time and dosage relationship of the action of 1 per cent saponin on rabbit's blood, the following experiments were performed in vitro. First, 9.0 c.c. of rabbit's citrated blood was placed in five graduated test tubes. Then at three-minute intervals 1.0 c.c. of 1 per cent saponin was added successively to each tube. At the end of fifteen minutes the five tubes along with a control were centrifuged for fifteen minutes at approximately 3,000 revolutions per minute. Then the packed cell volumes were determined, and the result was taken as the degree of hemolysis obtained.

In another experiment, varying amounts of saponin were added to tubes of blood each containing 9.0 c.c. of rabbit's citrated blood to make serial dilutions. These tubes of blood were allowed to stand for fifteen minutes, centrifuged for fifteen minutes at 3,000 revolutions per minute, and the degree of hemolysis determined from the remaining packed cell volumes.

RESULTS

In Vitro Experiment of 1 Per Cent Saponin and Citrated Rabbit Blood.—Laking of blood by saponin depends on its affinity for the lipoids of the cell envelope and stroma.[13] From the results of the in vitro experiments with 1 per cent saponin and citrated rabbit's blood, it is apparent that saponin acts rapidly, but only if it is present in sufficient concentration. It appears that the hemolysis obtained with smaller quantities of the 1 per cent saponin was probably due to the high concentration at the point and time of mixing. From these experiments, it would not be justifiable to assume that the amount of hemolysis obtained in any experiment was in any way proportional to the quantity of saponin given. Therefore, a quantity of 1 per cent saponin, which when given rapidly produces a marked hemolysis, may actually hemolyze a larger number of red blood cells than a greater quantity of saponin given more slowly.

The packed cell volume of citrated rabbit's blood was found to be approximately 30 to 35 per cent of the blood, as compared to 40 per cent packed cells when clotted blood was used.

Intravascular Laking by Saponin.—The experiments in which 1 per cent saponin was injected to produce intravascular hemolysis are summarized in Table I. It can be seen that when the hemolysis was rapid and fairly extensive, higher levels of serum potassium were obtained than when the hemolysis was more gradual or less extensive. If one assumes that the decrease in packed cell volume is roughly proportional to the percentage of red cells hemolyzed, it is noted that the degree of intravascular hemolysis found necessary to raise the concentration of the serum potassium from the normal of 4 meq. to 15 meq. per liter or more, varied from 12.5 to 65 per cent of the animal's blood cells, depending mainly on the rate and degree of the hemolysis. In Experiment 3, with a reduced rate of injection of the saponin producing a more gradual and perhaps less extensive hemolysis, the serum potassium did not rise above 8.5 meq. per liter at the end of sixty minutes. However, in Experiment 21, although the degree of hemolysis was approximately the same as in Experiment 3, the rate was much faster, and a level of serum potassium of 20 meq. per liter was obtained in twenty minutes.

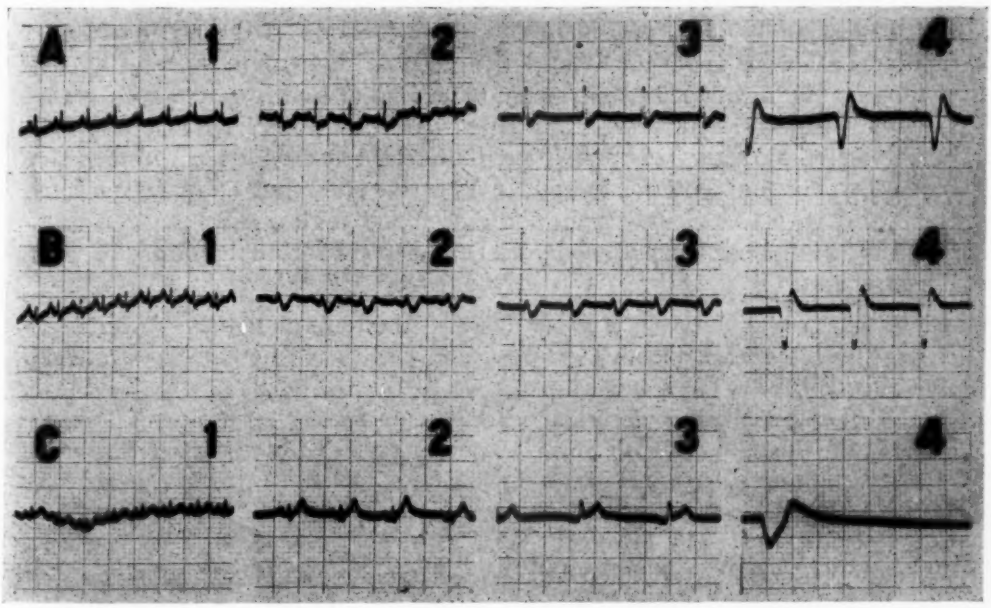


Fig. I.—*A*, *B*, and *C* are typical of the sequence of electrocardiographic changes obtained with injection of 1.0 per cent saponin (*A*), injection of human laked blood (*B*), and rabbit's laked red cells (*C*).

A, (*1*) Control, Lead II. (*2*) Elevated T wave, RS-T segment depressed, P waves present. (*3*) P waves have disappeared, RS-T segment depressed. (*4*) Early disorganization of the QRS complex.

B, (*1*) Control, Lead II. (*2*) Slight elevation of T wave, RS-T segment depressed, P wave present. (*3*) P waves have disappeared, RS-T segment depressed. (*4*) Early disorganization of QRS complex.

C, (*1*) Control, Lead II. (*2*) Marked elevation of T wave, only slight depression of RS-T segment. (*3*) Elevated T wave, P wave flattened but still present. (*4*) Terminal disintegration of entire QRS complex.

From the data in Table I, it can be seen that the electrocardiograms obtained reflected the concentration of the serum potassium. In Experiments 3 and 17, at concentrations of potassium between 5.9 and 8.5 meq. per liter, the electrocardiographic changes were limited to elevated or biphasic T waves, and RS-T segment depression (see Fig. 1,*A*). The loss of the P wave was noted at a concentration of 8.9 meq. per liter and higher. In Experiments 7, 13, and 21, at serum potassium levels of between 11.7 and 14.5 meq. per liter, the electrocardiograms showed elevation of the T wave, RS-T segment depression, loss of the P wave, and beginning widening of the QRS complex, but complete disintegration of the QRS complex was not yet apparent. Complete disintegration of the QRS complex and final cardiac arrest were observed only when the serum potassium levels were 14.9 meq. per liter and over, the average level being approximately 16.8 meq. per liter. The levels of serum potassium and the associated electrocardiographic changes noted in these experiments are very similar to those reported following the slow injection of isotonic potassium chloride in dogs[3] and in rabbits.[6]

Ventricular extrasystoles, ventricular tachycardia, and bigeminal rhythms were seen frequently in some experiments, and these were probably due to a toxic action of saponin. In Experiment 18, where the rate of hemolysis was very rapid, spontaneous ventricular fibrillation occurred four minutes from the start of the saponin injection, and the serum potassium at that instant was 13.3 mEq per liter. In Experiments 3, 17, and 20, ventricular fibrillation was precipitated by the insertion of the hypodermic needle into the heart for the withdrawal of blood for potassium determination. In Experiments 7 and 13, where no intratracheal oxygen was given, respiration ceased and the experiments were terminated before sufficient hemolysis had occurred to produce lethal levels of serum potassium.

Intravenous Injection of Human Blood.—The data of the experiments with citrated whole human blood (Group O) and with laked human blood are presented in Table II.

All the animals died of cardiac arrest within twenty-four minutes from the onset of the injection. Death in each case was preceded by the typical sequence of electrocardiographic changes as in the case of the saponin experiments (Fig. 1,*B*). Very high concentrations of serum potassium were found terminally in these experiments. The extremely high levels were due to the fact that there was a sudden partial to complete intravascular hemolysis of the rabbit's own cells as well as that of the donor cells (human).

Intravenous Injection of Laked Rabbit Cells.—In Table III are summarized the data in the experiment with the laked rabbit red cells. The potassium concentration in the laked red cell suspension was 32.0 mEq per liter.

Here again, terminally, the rabbits showed lethal levels of serum potassium with death by cardiac arrest. The electrocardiographic changes were again characteristic of potassium intoxication (Fig. 1,*C*). Although the total amount of laked red cells injected into Rabbits 22 and 23 was approximately the same, the faster rate of injection in Experiment 23 resulted in a higher level of serum potassium in a shorter time.

Control Studies.—In the rabbit made anoxic with excess Nembutal, as well as in the rabbit with the trachea clamped, electrocardiograms revealed some elevation of the T wave and RS-T segment depression. The complexes decreased in amplitude and varying degrees of heart block were noted terminally. In no instance was there a loss of the P wave or a broadening or disintegration of the QRS complex characteristic of potassium intoxication. The serum potassium determined terminally for the rabbit with the trachea clamped was 5.6 meq. per liter. In a series of electrocardiograms taken on four rabbits which were completely exsanguinated, the changes consisted of T-wave elevation, depression of the RS-T segment, and only in one instance was there a loss of the P wave, but the animal did not show disintegration of the QRS complex noted in the experiments with saponin and laked red cells. Terminally, these animals showed varying degrees of heart block. The serum potassium in one of the exsanguinated rabbits was terminally increased to 7.4 meq. per liter.

DISCUSSION

These experiments demonstrate that sudden intravascular hemolysis may liberate sufficient potassium to cause cardiac arrest. In all experiments, the correlation between the sequence of electrocardiographic changes and the concentrations of serum potassium resembled very closely that found in animals given slow intravenous injections of isotonic potassium chloride[3,6] (Fig. 1 *A*, *B*, and *C*).

Although there was no direct relation between the amount of saponin injected and the extent of hemolysis found, it has been noted that in those experiments where the saponin was given more quickly, the rate and degree of hemolysis was greater, and higher levels of serum potassium with corresponding electrocardiographic changes occurred sooner than when the saponin was given more slowly (Table I). This may be due partly to the fact that when the hemolysis was more gradual, the excess serum potassium had more time to diffuse into the remaining extracellular fluid or be excreted by the kidneys, and the serum potassium never reached such high levels. It would appear, therefore, that the rate and degree of intravascular hemolysis are the important factors in determining the level of serum potassium obtained.

Since the packed cell volume determinations were made on partially clotted blood, it is evident that the values for the amount of hemolysis obtained were probably less than the actual degree of hemolysis present in each case. However, it is significant that the range of hemolysis in these experiments is in close accord with the calculated range necessary to elevate the serum potassium to 15 meq. per liter.

Because of the relatively short duration of each experiment, the ligation of the ureters in Rabbits 2, 3, 5, and 8 did not significantly affect the final outcome of these experiments.

The ventricular extrasystoles, ventricular tachycardia, and the beginimal rhythm, noted only in the saponin experiments, were probably due to saponin, a plant glucoside; but the spontaneous ventricular fibrillation noted in Experiment 18 was probably precipitated by the sudden elevation of the serum potas-

sium to 13.4 meq. per liter. Similar observations were made when isotonic chloride was rapidly injected into rabbits.[6]

Saponin can cause paralysis of the respiratory center,[13] as was noted in some of our experiments, but the use of continuous intratracheal oxygen tended to prevent anoxia. The observation had been previously made by Gottdenker[12] that in rabbits, doses of saponin of 20 mg. per kilogram of body weight resulted in death associated with extreme degrees of cardiac dilatation. However, applied to isolated strips of auricular muscle, saponin caused arrhythmias and ultimately death in contraction. It thus seems likely that the cardiac dilatation observed by Gottdenker was probably due to the terminal cardiac arrest in diastole caused by the excess serum potassium from the intravascular hemolysis.

Terminal serum potassium levels in the anoxic control rabbits were only slightly elevated, and electrocardiograms did not show the sequence of changes seen in potassium intoxication. These small elevations of serum potassium are in accord with the observations of Mullen, Dennis, and Calvin,[14] who found an increase of serum potassium up to 30 per cent of the original value in anoxic dogs. Scudder[15] also found similar small increases in serum potassium in cases of shock due to hemorrhage. Therefore, it may safely be assumed that any degree of anoxia present in these experiments did not raise the serum potassium sufficiently to account for the high levels of potassium and the associated electrocardiographic changes obtained.

The mechanism of death in cases of acute intravascular hemolysis is still not fully understood. The results of these experiments suggest that the sudden and extensive hemolysis seen in some cases of incompatible transfusion reaction, in erythroblastosis fetalis, and in cases of acute intravascular hemolysis from other causes can cause death from potassium intoxication. It is also obvious that impairment of renal function sufficient to prevent excretion of excess potassium will increase the possibility of lethal levels of serum potassium being reached.[16]

CONCLUSIONS

1. It has been shown that in rabbits, rapid intravascular hemolysis of red cells, by liberation of the intracellular potassium into the plasma, can cause death by potassium intoxication.

2. The possible implication of this in clinical cases of intravascular hemolysis has been discussed.

The authors wish to thank A. O. Denstedt for assistance and helpful suggestions.

REFERENCES

1. Kerr, S. E.: Studies on the Inorganic Composition of Blood. IV. The Relationship of Potassium to the Acid-Soluble Phosphorus Fractions, J. Biol. Chem. **117**:227, 1937.
2. Ringer, S.: A Further Contribution Regarding the Influence of the Different Constituents of the Blood on the Contraction of the Heart, J. Physiol. **4**:29, 1883.
3. Winkler, A. W., Hoff, H. E., and Smith, P. K.: Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injection of Potassium Chloride, Am. J. Physiol. **124**:478, 1938.
4. Hoff, H. E., Smith, P. K., and Winkler, A. W.: The Cause of Death in Experimental Anuria, J. Clin. Investigation **20**:607, 1941.

5. Finch, C. A., and Marchand, J. F.: Cardiac Arrest by the Action of Potassium, Am. J. M. Sc. **206**:507, 1943.
6. Nahum, L. H., and Hoff, H. E.: Observations on Potassium Fibrillation, J. Pharmacol. & Exper. Therap. **65**:322, 1939.
7. Keith, N. M., Burchell, H. B., and Baggenstoss, A. H.: Electrocardiographic Changes in Uremia Associated With a High Concentration of Serum Potassium, AM. HEART J. **27**:817, 1944.
8. Finch, C. A., Sawyer, C. G., and Flynn, J. M.: Clinical Syndrome of Potassium Intoxication, Am. J. Med. **1**:337, 1946.
9. Bywaters, E. G. L.: Ischemic Muscle Necrosis, J. A. M. A. **124**:1103, 1944.
10. Langendorf, R., and Pirani, C. L.: The Heart in Uremia, AM. HEART J. **33**:282, 1947.
11. Roos, A., Weisiger, J. R., and Moritz, A. R.: Physiological Mechanisms Responsible for Death During Intravenous Exposure to Excessive Heat, J. Clin. Investigation **26**:505-518, 1947.
12. Gottdenker, F.: Ueber die Wirkung von Saponin auf Herz und Krieslauf des Warmbluters, Arch. f. exper. Path. u. Pharmakol. **188**:538, 1937.
13. Sollman, T.: A Manual of Pharmacology, ed. 6, Philadelphia, 1942, W. B. Saunders Company, p. 556.
14. Mullen, F. J., Dennis, J., and Calvin, D. B.: Blood Potassium in Tetany and Asphyxia of Dogs, Am. J. Physiol. **124**:192, 1938.
15. Scudder, J.: Shock: Blood Studies as a Guide to Therapy, Montreal, 1940, J. B. Lippincott Company, p. 128.
16. Keith, N. M., King, H. E., and Osterberg, A. E.: Serum Concentration and Renal Clearance of Potassium in Severe Renal Insufficiency in Man, Arch. Int. Med. **71**:675, 1943.
17. Neufeld, A. H.: Personal communication.

AN ANALYSIS OF THE RELATIVE ACCURACIES OF THE WILSON AND GOLDBERGER METHODS FOR REGISTERING UNIPOLAR AND AUGMENTED UNIPOLAR ELECTROCARDIOGRAPHIC LEADS

MAURICE B. RAPPAPORT, E.E.,* AND CONGER WILLIAMS, M.D.†
With the Editorial Assistance of Paul D. White, M.D.†
BOSTON, MASS.

INTRODUCTION

A UNIPOLAR electrocardiographic lead is a graphic representation of the cardiac action potentials which are present at one particular location on a subject's body with respect to a nonfluctuating reference. It is differentiated from the usual bipolar electrocardiographic lead, for example, Lead I, in which the action potentials of the right and left arms fluctuate and the resultant electrocardiogram is an algebraic addition of these potentials with respect to time.

In 1932 Wilson, Johnston, Macleod, and Barker[1,2] suggested that a central terminal or nonfluctuating reference for unipolar leads may be obtained by connecting the right arm, left arm, and left leg to a junction point via three equal resistances. They suggested that the accuracy of the method is dependent upon the validity of the equilateral triangle of Einthoven, Fahr, and De Waart[3] and Kirchhoff's[4] laws of electric networks.

Kirchhoff's two laws pertaining to electric networks were first formulated in 1845. They are special expressions of relations explicit in field equations applicable to electric circuits. The first law, known as the voltage law, states: *If in an electric network a closed path is traversed, the algebraic sum of voltages across the individual elements in the direction of traversal is zero.* The second law, known as the current law, states: *The algebraic sum of all currents directed toward and away from a junction is zero* because electricity behaves like an incompressible fluid. By means of Kirchhoff's laws it is possible to determine the resultant behavior of any lumped-parameter linear electric network such as a unipolar electrocardiographic lead.

Wilson, Johnston, Macleod, and Barker observed that according to Kirchhoff's second law the potential of the junction or central terminal must be equal at every instant to the mean of the potentials of the electrodes on the right arm, left arm, and left leg. If the assumption is now made that the equilateral triangle of Einthoven, Fahr, and De Waart is valid and that the electrical forces of cardiac origin which are perpendicular to the plane formed by the limb leads

*From the Research Department, Sanborn Company.
†From the Cardiac Laboratory, Massachusetts General Hospital.

have negligible effect upon the variations in potential at the limbs, then the central terminal cannot be materially affected by the action potentials throughout the cardiac cycle.

The validity of Kirchhoff's laws as applied to central terminal calculation is unquestionable. They are universally employed and accepted as an important tool by the mathematical physicist and electrical engineer for the calculation of electric networks. The application of Kirchhoff's laws to the central terminal circuit is comparatively simple and straightforward. On the other hand, there has been controversial discussion[5,6] as to the validity of the equilateral triangle of Einthoven, Fahr, and De Waart. Unfortunately, it is most difficult to prove the validity of the equilateral triangle by mathematical means because of the extremely complex nature of the electrical field produced by the heart beat. As a result, experimental methods have been employed by a number of investigators.[7,8,9,10] The general procedure employed by Fahr and Weber,[7] Wagner,[8] and Johnston, Kossmann, and Wilson[9] was to apply constant or variable potentials via two metallic electrodes inserted in the heart of a cadaver and to compute from the differences in potential in the limb leads whether the relationships expressed in the equilateral triangle of Einthoven, Fahr, and De Waart hold true. Wilson and Herrmann[10] stimulated the heart of a living dog by means of an inductorium connected to two electrodes in the ventral wall of the heart, one near the base and the other near the apex. The electrodes were so located that a line joining them was very nearly parallel to the long axis of the body. *All of the investigators found that the direction and relative magnitude of the deflections in the limb leads were comparable, within close limits, with the relationships expressed in the equilateral triangle theory.*

Burger and Whurmann[11] compared the central terminal of the Einthoven, Fahr, and De Waart triangle with that of other central terminals, each connected to a set of three electrodes located equidistant from the heart and lying at the apices of a triangle enclosing it. They observed that the potential differences between the various central terminals were practically zero. Wilson and his co-workers[12] carried out similar experiments. They state: "Arrighi is known to have carried out experiments of a similar kind. So far as we know, his work has not yet been published, but all of his experiments that we have knowledge of yielded results comparable to those reported by Burger and Wuhrmann. We have performed one experiment of the same kind and the results of such experiments are predictable on the basis of Arrighi's[13] published work." Wilson and associates[12] employed the Arrighi triangle and compared its potential with that of the equilateral triangle of Einthoven, Fahr, and De Waart and found that the difference in potential did not exceed 0.15 millivolt. The Arrighi triangle is obtained as follows: one electrode is placed in the left submaxillary region close to the chin, the second 3.0 or 4.0 cm. to the left of the midpoint of a line joining the umbilicus with the center of the pubis, and a third in the left interscapular space, approximately at the level of the spinous process of the seventh thoracic vertebra.

A possible source of error in the application of the Einthoven triangle hypothesis to unipolar electrocardiography lies in the position of the frontal

plane determined by the three reference points (right arm, left arm, and left leg). Some doubt has been expressed as to the inclusion of the center of electrical activity of the heart in the frontal plane. If this plane does not pass through the center of electrical activity, the potential of the central terminal will be positive or negative, depending upon the spatial relationship of the heart to the plane in an electrical sense.

Eckey and Fröhlich,[15] Burger,[16] and Wilson and associates[12] have performed immersion experiments to ascertain the degree of potential fluctuation that may occur between the central terminal formed by the Einthoven equilateral triangle and the central terminal by immersion. Eckey and Fröhlich employed distilled water and completely immersed the subject in a metal-lined tub; the subject was allowed to breathe through a tube. The electrodes employed for obtaining the central terminal formed by the right arm, left arm, and left leg were not insulated from the distilled water; the immersion central terminal was the metal lining of the tub. Eckey and Fröhlich observed a slight modification in the limb lead deflections after immersion due to the slight electrical conductivity of the distilled water. The greatest variations in potential observed between the two central terminals in an unspecified number of experiments was of the order 0.3 millivolt. Burger employed a zinc tub filled with tap water, but the subject's face was not immersed and the limb electrodes were insulated from the water. Burger observed a 25 per cent reduction in the standard limb lead deflections which may be ascribed to the conductivity of tap water. In five normal subjects the greatest potential difference between the two central terminals was approximately 0.26 millivolt. Wilson and associates immersed the subject up to the neck in a fresh-water lake. The immersion central terminal was a large metal electrode suspended in the lake approximately eleven feet from the body. The short-circuiting effect of the lake water reduced the standard limb lead deflections approximately 50 per cent. The largest potential variation measured between the two central terminals was 0.15 millivolt. These authors did not state whether the limb electrodes were insulated from the water. They concede that a certain degree of error is present in the immersion experiments but conclude that the central terminal formed by the right arm, left arm, and left leg is a good approximation of a nonfluctuating reference.

In 1942 Goldberger[14] suggested that unipolar electrocardiographic leads may be obtained by means of the Wilson technique, with the exception that the central terminal be formed by connecting the right arm, left arm, and left leg directly to a junction point without interposing the 5,000 ohm resistors. In other words, the Goldberger method depends entirely upon the subject resistance in each limb. Wilson and his co-workers[1,2] at first thought that 25,000 ohm resistors in each limb circuit would produce a central terminal more nearly unipotential. They decided, however, to use 5,000 ohms because of the greater susceptibility of the electrocardiographic apparatus to alternating current interference when 25,000 ohm resistors are employed. *The purpose of the resistors in each limb circuit is to minimize differences in subject resistance at each limb. Theoretically, dissimilarity in contact resistance of each limb introduces variation in*

current distribution in the central terminal circuit which affects the potential of the central terminal.

The Goldberger modification is widely employed in clinical electrocardiography. In this paper it is our object to show mathematically the relative accuracies of the Wilson and Goldberger methods. An actual comparison of unipolar electrocardiograms taken with Wilson and Goldberger leads was made by Bryant and Johnston[19,20] in a series of 500 cases, using only the left leg lead (aV_F). A significant difference between the Wilson and Goldberger techniques was observed in 10 per cent of the cases.

We are in the process of a more extensive investigation in which a comparison of the electrocardiograms taken with both techniques is being made. In addition, the actual measurement of the resistances as they exist at the points of contact of electrodes to the limbs is being made. These results will be published in subsequent papers.

THE CENTRAL TERMINAL

The basic circuit of a central terminal in which the resistances in the three limb circuits are equal is shown in Fig. 1. This condition occurs in the Wilson method when the patient resistances of each limb are identical and each is in series with a 5,000 ohm resistor. That is, R is equal to limb resistance plus 5,000 ohms. When the Goldberger method is employed, the condition of Fig. 1 occurs when the patient resistances of the limbs are equal. That is, R is equal to the resistance of each limb. Let

e_0 = voltage at the central terminal as a result of cardiac action
e_1 = instantaneous voltage at the right arm electrode as a result of cardiac action
e_2 = instantaneous voltage at the left arm electrode as a result of cardiac action
e_3 = instantaneous voltage at the left leg electrode as a result of cardiac action
E_1 = instantaneous voltage between the right arm electrode and the central terminal
i_1 = current flow between right arm electrode and central terminal
i_2 = current flow between left arm electrode and central terminal
i_3 = current flow between left leg electrode and central terminal

The arrows associated with current flow are arbitrarily assumed according to Kirchhoff's second law. According to Ohm's law, which states that the current in a conducting system at any instant is equal to the applied voltage divided by the resistance offered to the flow of current, we may state that in Fig. 1

$$i_1 = \frac{e_1 - e_0}{R} \qquad [1]$$

$$i_2 = \frac{e_2 - e_o}{R} \qquad [2]$$

$$i_3 = \frac{e_o - e_3}{R} \qquad [3]$$

From the indicated direction of current flow in Fig. 1,

$$i_3 = i_1 + i_2 \qquad [4]$$

Substituting Equations 1, 2, and 3 in Equation 4

$$\frac{e_o - e_3}{R} = \frac{e_1 - e_o}{R} + \frac{e_2 - e_o}{R}$$

$$\therefore \qquad 3\,e_o = e_1 + e_2 + e_3$$

or

$$e_o = \frac{e_1 + e_2 + e_3}{3} \qquad [5]$$

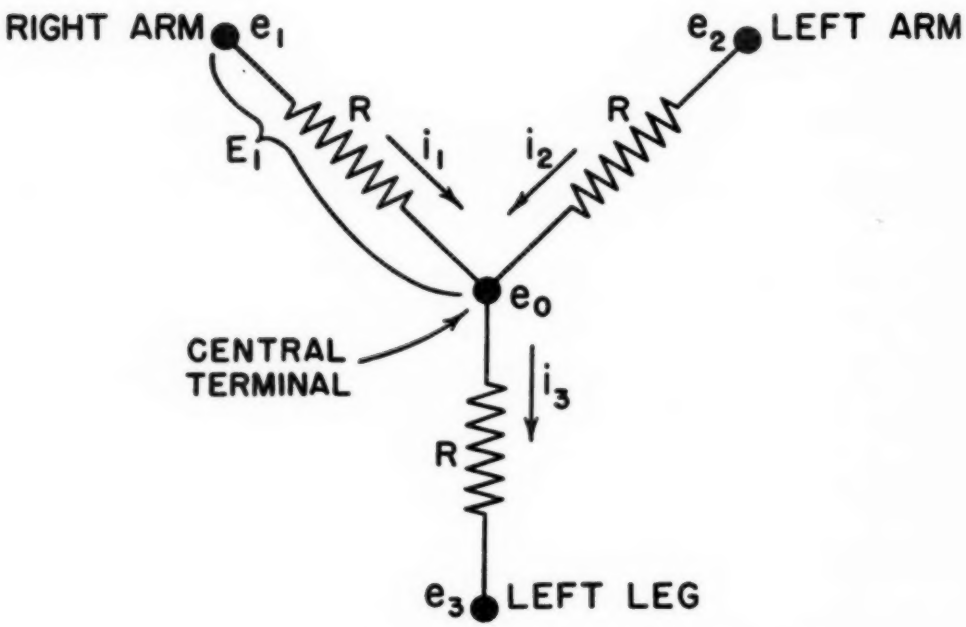


Fig. 1.—The basic circuit of a central terminal in which the resistances in the three limb circuits are equal.

Equation 5 is the Wilson, Macleod, and Barker formula which states that the potential of the central terminal must be equal at every instant to the mean of the potentials of the electrodes on the right arm, left arm, and left leg. Also

$$E_1 = e_1 - e_o \qquad [6]$$

By substituting Equation 5 into Equation 6, we get

$$E_1 = e_1 - \left[\frac{e_1 + e_2 + e_3}{3}\right]$$

or

$$E_1 = e_1 - \frac{e_1}{3} - \frac{e_2}{3} - \frac{e_3}{3} \qquad [7]$$

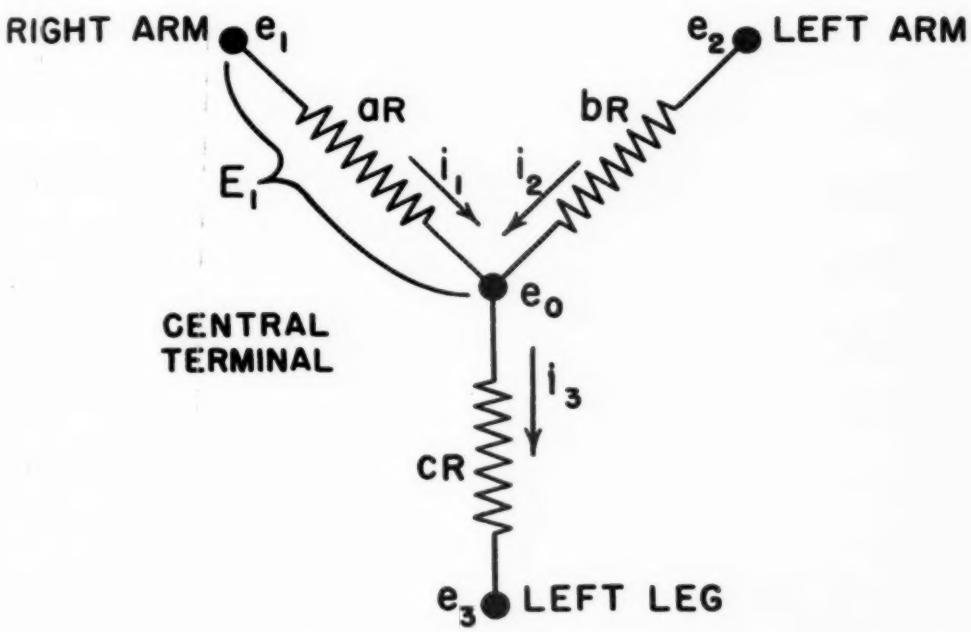


Fig. 2.—The basic circuit of a central terminal in which the resistances in the three limb circuits are dissimilar because of differences in the resistance of the right arm, left arm, and left leg.

Let us now consider the Wilson circuit in Fig. 2 where unlike values of patient resistance are present in each limb circuit. If we let

a, b, and c = factors which, when multiplied by the nominal limb circuit resistance R, give the actual limb circuit resistance,

then

$$i_1 = \frac{e_1 - e_o}{aR} \qquad [8]$$

$$i_2 = \frac{e_2 - e_o}{bR} \qquad [9]$$

$$i_3 = \frac{e_o - e_3}{cR} \qquad [10]$$

also $$i_3 = i_1 + i_2 \qquad [11]$$

By substituting Equations 8, 9, and 10 in Equation 11 we get

$$\frac{e_o - e_3}{cR} = \frac{e_1 - e_o}{aR} + \frac{e_2 - e_o}{bR}$$

$$\therefore \quad \frac{e_1}{a} + \frac{e_2}{b} + \frac{e_3}{c} = \frac{e_o}{a} + \frac{e_o}{b} + \frac{e_o}{c}$$

$$\frac{e_1}{a} + \frac{e_2}{b} + \frac{e_3}{c} = e_o \left[\frac{1}{a} + \frac{1}{b} + \frac{1}{c}\right]$$

$$\frac{e_1}{a} + \frac{e_2}{b} + \frac{e_3}{c} = e_o \left[\frac{bc + ac + ab}{abc}\right]$$

or $$e_o = \left[\frac{e_1}{a} + \frac{e_2}{b} + \frac{e_3}{c}\right]\left[\frac{abc}{bc + ac + ab}\right]$$

$$\therefore \quad e_o = \frac{bce_1 + ace_2 + abe_3}{bc + ac + ab} \qquad [12]$$

A reasonable assumption is that the following values of patient resistance may exist in a hypothetical case

right arm = *1,000 ohms*
left arm = *2,000 ohms*
left leg = *3,000 ohms*

Therefore,

$a = 1/2$
$b = 1$
$c = 3/2$

If we substitute these values of patient resistance in Equation 12 we get

$$e_o = \frac{\frac{3}{2}e_1 + \frac{3}{4}e_2 + \frac{1}{2}e_3}{\frac{3}{2} + \frac{3}{4} + \frac{1}{2}} = \frac{\frac{3}{2}e_1 + \frac{3}{4}e_2 + \frac{1}{2}e_3}{\frac{11}{4}} \qquad [13]$$

If we now take a case where the instantaneous voltages at the three limb electrodes are

$$\begin{aligned} \textit{right arm} &= e_1 = -1.2\ mv. \\ \textit{left arm} &= e_2 = +0.9\ mv. \\ \textit{left leg} &= e_3 = +0.3\ mv. \end{aligned}$$

According to Equation 5, the theoretically correct voltage at the central terminal as a result of cardiac action is

$$e_o \text{ [Theoretical]} = \frac{e_1 + e_2 + e_3}{3} = \frac{-1.2 + 0.9 + 0.3}{3} = 0\ mv.$$

which is the mean value of the potentials at the three limbs.

According to equation 13

$$e_o \text{ [Goldberger]} = \frac{-\frac{3}{2} \times 1.2 + \frac{3}{4} \times 0.9 + \frac{1}{2} \times 0.3}{\frac{11}{4}} = -0.355\ mv.$$

In the Wilson central terminal the resistance in the

$$\begin{aligned} \textit{right arm circuit} &= 1{,}000 + 5{,}000 = 6{,}000\ ohms \\ \textit{left arm circuit} &= 2{,}000 + 5{,}000 = 7{,}000\ ohms \\ \textit{left leg circuit} &= 3{,}000 + 5{,}000 = 8{,}000\ ohms \end{aligned}$$

Thus,

$$\begin{aligned} a &= 6/7 \\ b &= 1 \\ c &= 8/7 \end{aligned}$$

If we substitute these values into Equation 12 we get

$$e_o \text{ [Wilson at 5,000 ohms]} = \frac{-1 \times \frac{8}{7} \times 1.2 + \frac{6}{7} \times \frac{8}{7} \times 0.9 + \frac{6}{7} \times 1 \times 0.3}{1 \times \frac{8}{7} + \frac{6}{7} \times \frac{8}{7} + \frac{6}{7} \times 1} = -0.077\ mv.$$

When 10,000 ohm resistors are employed in the Wilson central terminal instead of 5,000 ohms, then

$$\begin{aligned} \textit{right arm circuit} &= 1{,}000 + 10{,}000 = 11{,}000\ ohms \\ \textit{left arm circuit} &= 2{,}000 + 10{,}000 = 12{,}000\ ohms \\ \textit{left leg circuit} &= 3{,}000 + 10{,}000 = 13{,}000\ ohms \end{aligned}$$

Therefore,

$$a = 11/12$$
$$b = 1$$
$$c = 13/12$$

If we substitute these values in Equation 12, we get

$$e_o \text{ [Wilson at 10,000 ohms]} = \frac{-1 \times \frac{13}{12} \times 1.2 + \frac{11}{12} \times \frac{13}{12} \times 0.9 + \frac{11}{12} \times 1 \times 0.3}{1 \times \frac{13}{12} + \frac{11}{12} \times \frac{13}{12} + \frac{11}{12} \times 1} = -0.043 \text{ mv.}$$

Our calculations show, therefore,

Theoretically correct voltage at central terminal = 0 mv.
Wilson central terminal voltage employing 10,000 ohm resistors = −0.043 mv.
Wilson central terminal voltage employing 5,000 ohm resistors = −0.077 mv.
Goldberger central terminal voltage = −0.355 mv.

E_1 is the instantaneous voltage between the right arm and the central terminal or what is clinically termed as the V_R or right unipolar limb lead. The effect on this lead by the unbalance due to unequal patient resistance in the right arm, left arm, and left leg may be calculated in the following manner:

$$E_1 \text{ [Theoretical]} = e_1 - e_o = -1.2 + 0 = -1.2 \text{ mv.}$$

$$E_1 \text{ [Wilson at 10,000 ohms]} = -1.2 + 0.043 = -1.157 \text{ mv.}$$

$$E_1 \text{ [Wilson at 5,000 ohms]} = -1.2 + 0.077 = -1.123 \text{ mv.}$$

$$E_1 \text{ [Goldberger]} = -1.2 + 0.355 = -0.845 \text{ mv.}$$

The voltage errors introduced in the V_R lead by the Wilson and Goldberger methods are:

Wilson central terminal with 10,000 ohm resistors = 3.59 per cent error
Wilson central terminal with 5,000 ohm resistors = 6.42 per cent error
Goldberger central terminal = 29.5 per cent error

THE AUGMENTED UNIPOLAR EXTREMITY LEADS

Unipolar extremity leads as taken with the original Wilson technique are usually of rather low magnitude. To facilitate a reasonable degree of accuracy in the reading of the graph, it is usually desirable to increase the sensitivity of the

electrocardiograph to 1.5 or 2 cm. per millivolt. *Goldberger*[14] *suggested that all complexes in unipolar extremity leads are increased by a factor of 1.5 if the connection from the central terminal is removed from the limb under investigation.* Goldberger suggested that the extremity lead which is registered with an increased magnitude of 1.5 times normal be called the *augmented unipolar extremity lead* and be symbolized as follows:

aV_R = augmented unipolar right arm
aV_L = augmented unipolar left arm
aV_F = augmented unipolar left leg

Let us now determine by mathematical calculation the accuracy of Goldberger's relationship. Fig. 3 is a representation of the basic electrical circuit which is created when an augmented unipolar right arm lead is taken as suggested by Goldberger. Let us also assume an ideal condition in which the patient resistances in the left arm and left leg are equal. Then

e'_o = voltage at the central terminal as a result of cardiac action
E'_1 = instantaneous potential difference between right arm and central terminal which is the aV_R lead
E_1 = instantaneous potential difference between right arm and central terminal representing the unipolar right extremity (V_R) lead of Fig. 2
e_1 = instantaneous potential at right arm electrode as a result of cardiac action
e_2 = instantaneous potential at left arm electrode as a result of cardiac action
e_3 = instantaneous potential at left leg electrode as a result of cardiac action

From Fig. 3 it is obvious that

$$e'_o = \frac{e_2 + e_3}{2} \qquad [14]$$

also $$E'_1 = e_1 - e'_o \qquad [15]$$

If we substitute Equation 14 into Equation 15, we get

$$E'_1 = e_1 - \left[\frac{e_2 + e_3}{2}\right] = e_1 - \frac{e_2}{2} - \frac{e_3}{2} \qquad [16]$$

But $$E'_1 - E_1 = aV_R\ lead - V_R\ lead \qquad [17]$$

Using Equations 16 and 7, we may say that

$$E'_1 - E_1 = e_1 - \frac{e_2}{2} - \frac{e_3}{2} - e_1 + \frac{e_1}{3} + \frac{e_2}{3} + \frac{e_3}{3}$$

$$E'_1 - E_1 = \frac{e_1}{3} - \frac{e_2}{6} - \frac{e_3}{6} = \frac{1}{3}\left[e_1 - \frac{e_2}{2} - \frac{e_3}{2}\right]$$

or $$E'_1 - E_1 = \frac{1}{3} E'_1$$

$$\therefore \quad E'_1 = \frac{3}{2} E_1 = 1.5\, E_1 \qquad [18]$$

The derivation of Equation 18 is a mathematical proof which substantiates Goldberger's relationship that the aV_R lead is identical in configuration to the V_R lead but increased by a factor of 1.5 when the patient resistances in the left arm and left leg are identical.

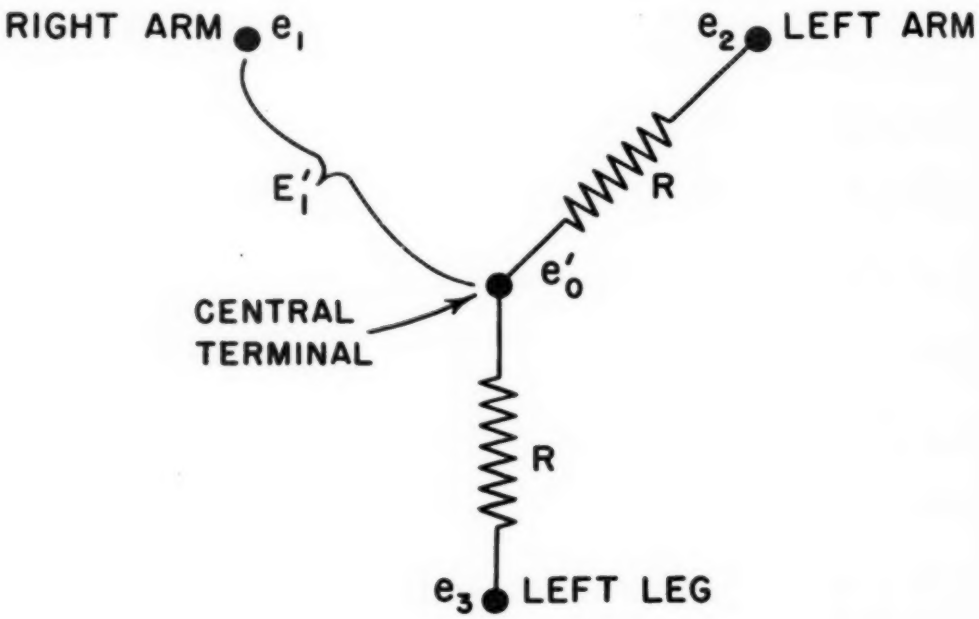


Fig. 3.—The basic circuit of an augmented unipolar right arm lead in which the patient resistances in the left arm and left leg circuits are equal.

From Fig. 3 and the preceding calculation on the augmented unipolar extremity leads it is obvious that the Wilson central terminal may be used exactly like the Goldberger central terminal to obtain the aV_R, aV_L, and aV_F leads. The basis for this assumption is that R in Fig. 3 is merely the sum of limb resistance plus the value of the resistor in the Wilson central terminal circuit and the mathematical derivation is thus unaffected.

Let us now consider the effects of dissimilar patient resistance in the extremities. In the calculations that are to follow we may assume that in Fig. 4

e_1 = instantaneous potential at right arm electrode as a result of cardiac action
e_2 = instantaneous potential at left arm electrode as a result of cardiac action
e_3 = instantaneous potential at left leg electrode as a result of cardiac action
e''_o = voltage at the central terminal as a result of cardiac action
E''_1 = instantaneous potential difference between right arm and central terminal which is the aV_R lead
bR = resistance of left arm circuit
cR = resistance of left leg circuit
i = current flow as a result of cardiac action

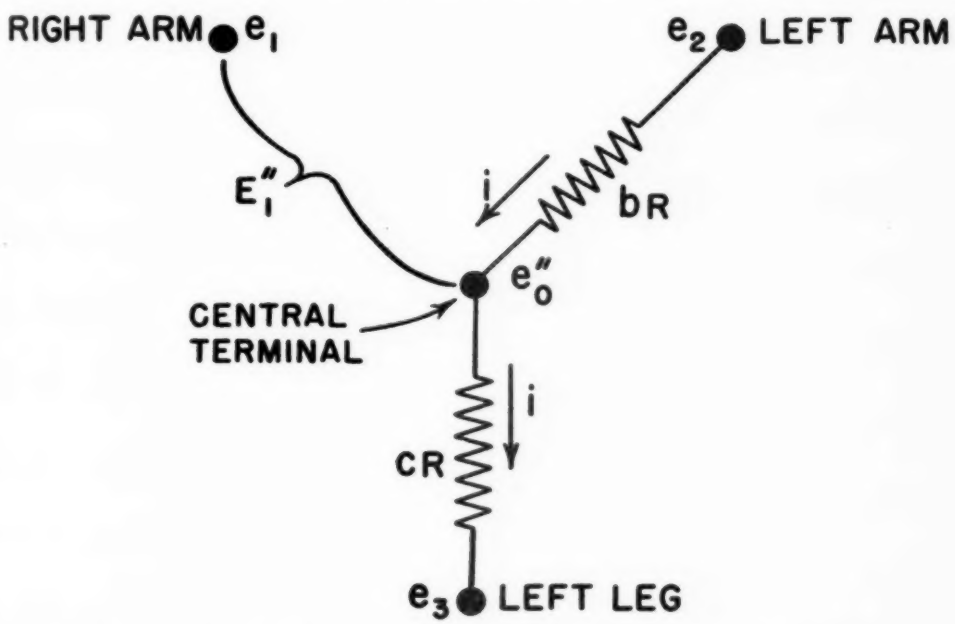


Fig. 4.—The basic circuits of an augmented unipolar right arm lead in which the patient resistances in the left arm and left leg circuits are not alike.

According to Ohm's law

$$i = \frac{e_2 - e''_o}{bR} = \frac{e''_o - e_3}{cR} \qquad [19]$$

cancelling out R we get

$$\frac{e_2 - e''_o}{b} = \frac{e''_o - e_3}{c}$$

$$\frac{e_2}{b} - \frac{e''_o}{b} = \frac{e''_o}{c} - \frac{e_3}{c}$$

$$\frac{e_2}{b} + \frac{e_3}{c} = \frac{e''_o}{c} + \frac{e''_o}{b} = e''_o \left[\frac{1}{c} + \frac{1}{b}\right]$$

or

$$e''_o = \frac{\frac{e_2}{b} + \frac{e_3}{c}}{\frac{1}{c} + \frac{1}{b}} = \frac{e_2 c + e_3 b}{b + c} \qquad [20]$$

As previously, let patient resistance in

left arm = 2,000 ohms
left leg = 3,000 ohms

Also as before, let

$e_2 = 0.9$ *mv.*
$e_3 = 0.3$ *mv.*

According to Equation 14, the theoretically correct augmented central terminal voltage is

$$e''_{o\ [\text{Theoretical}]} = \frac{e_2 + e_3}{2} = \frac{0.9 + 0.3}{2} = 0.6 \text{ mv.}$$

If the Wilson central terminal composed of 10,000 ohm resistors is used to obtain the augmented unipolar limb lead, the resistance of

left arm = 2,000 + 10,000 = 12,000 ohms
left leg = 3,000 + 10,000 = 13,000 ohms

Thus,

$b = 1$
$c = 13/12$

According to Equation 20, the augmented central terminal voltage by the Wilson technique with 10,000 ohm resistors is

$$e''_{o\ [\text{Wilson at 10,000 ohms}]} = \frac{c_2 c + e_3 b}{b + c} = \frac{0.9 \times \frac{13}{12} + 0.3 \times 1}{1 + \frac{13}{12}} = 0.612 \text{ mv.}$$

When the Wilson technique with 5,000 ohm resistors is used,

left arm = 2,000 + 5,000 = 7,000 ohms
left leg = 3,000 + 5,000 = 8,000 ohms

Thus,

$$b = 1$$
$$c = 8/7$$

$$\text{or} \quad e''_o \text{ [Wilson at 5,000 ohms]} = \frac{0.9 \times \frac{8}{7} + 0.3 \times 1}{1 + \frac{8}{7}} = 0.62 \text{ mv.}$$

If the Goldberger technique is used

$$\text{left arm} = 2{,}000 \text{ ohms}$$
$$\text{left leg} = 3{,}000 \text{ ohms}$$

Thus,

$$b = 1$$
$$c = 3/2$$

$$\text{or} \quad e''_o \text{ [Goldberger]} = \frac{0.9 \times \frac{3}{2} + 0.3 \times 1}{1 + \frac{3}{2}} = 0.66 \text{ mv.}$$

Our calculations therefore show:

Theoretically correct voltage at central terminal = 0.6 mv.
Wilson central terminal voltage employing 10,000 ohm resistors = 0.612 mv.
Wilson central terminal voltage employing 5,000 ohm resistors = 0.62 mv.
Goldberger central terminal voltage = 0.66 mv.

E'' is the instantaneous potential difference between the right arm and the central terminal which is the aV_R lead or augmented unipolar right limb lead. The effect on this lead by patient resistance unbalance in the left arm and left leg circuits may be calculated in the following manner:

E''_1 [Theoretical] $= e_1 - e''_0 = -1.2 - 0.6 = -1.8$ mv.
E''_1 [Wilson at 10,000 ohms] $= -1.2 - 0.612 = -1.812$ mv.
E''_1 [Wilson at 5,000 ohms] $= -1.2 - 0.62 = -1.82$ mv.
E''_1 [Goldberger] $= -1.2 - 0.66 = -1.86$ mv.

The voltage error introduced in the aV_R lead by the Wilson and Goldberger methods is:

Wilson method with 10,000 ohm resistors = 0.67 per cent error
Wilson method with 5,000 ohm resistors = 1.1 per cent error
Goldberger method = 3.3 per cent error

It so happens, that in this case the patient resistance discrepancy between the left arm and left leg is not as great as occurs between the right arm and left leg. If the aV_L lead were taken in this hypothetical case, the patient resistance factor should be of greater consequence. For comparative purposes, however, we may calculate the error in the aV_R lead if the left arm patient resistance is 1,000 ohms instead of 2,000 ohms. Thus,

$$\textit{left arm} = 1{,}000 \text{ ohms}$$
$$\textit{left leg} = 3{,}000 \text{ ohms}.$$

As before,

$$e_2 = 0.9 \text{ mv}.$$
$$e_3 = 0.3 \text{ mv}.$$

According to Equation 14, the theoretically correct augmented central terminal still is

$$e''_o \text{ [Theoretical]} = \frac{e_2 + e_3}{2} = \frac{0.9 + 0.3}{2} = 0.6 \text{ mv}.$$

If the Wilson central terminal composed of 10,000 ohm resistors is used to obtain Lead aV_R, the resistance of

$$\textit{left arm circuit} = 1{,}000 + 10{,}000 = 11{,}000 \text{ ohms}$$
$$\textit{left leg circuit} = 3{,}000 + 10{,}000 = 13{,}000 \text{ ohms}$$

Thus,

$$b = 1$$
$$c = 13/11$$

According to Equation 20, the augmented central terminal voltage by the Wilson technique with 10,000 ohm resistors is

$$e''_o \text{ [Wilson at 10,000 ohms]} = \frac{0.9 \times \frac{13}{11} + 0.3 \times 1}{1 + \frac{13}{11}} = 0.623 \text{ mv}.$$

When the Wilson technique with 5,000 ohm resistors is used,

$$\textit{left arm circuit} = 1{,}000 + 5{,}000 = 6{,}000 \text{ ohms}$$
$$\textit{left leg circuit} = 3{,}000 + 5{,}000 = 8{,}000 \text{ ohms}$$

Thus,

$$b = 1$$
$$c = 8/6$$

or

$$e''_{o\ \text{[Wilson at 5,000 ohms]}} = \frac{0.9 \times \frac{8}{6} + 0.3 \times 1}{1 + \frac{8}{6}} = 0.644\ mv.$$

When the Goldberger technique is used

left arm circuit = *1,000 ohms*
left leg circuit = *3,000 ohms*

Thus,

$b = 1$
$c = 3$

or $$e''_{o\ \text{[Goldberger]}} = \frac{0.9 \times 3 + 0.3 \times 1}{1 + 3} = 0.75\ mv.$$

Our calculations therefore show:

Theoretically correct voltage at central terminal = 0.6 mv.
Wilson central terminal voltage employing 10,000 ohm resistors = 0.623 mv.
Wilson central terminal voltage employing 5,000 ohm resistors = 0.644 mv.
Goldberger central terminal voltage = 0.75 mv.

E'' is the instantaneous potential difference between the right arm and the central terminal which is the aV_R lead. The effect on this lead by patient resistance unbalance in the left arm and left leg circuits is:

E''_1 [Theoretical] $= e_1 - e''_o = -1.2 - 0.6 = -1.8\ mv.$
E''_1 [Wilson at 10,000 ohms] $= -1.2 - 0.623 = -1.823\ mv.$
E''_1 [Wilson at 5,000 ohms] $= -1.2 - 0.644 = -1.844\ mv.$
E''_1 [Goldberger] $= -1.2 - 0.75 = -1.95\ mv.$

The voltage error introduced in the aV_R lead by the Wilson and Goldberger methods is:

Wilson method with 10,000 ohm resistors = 1.28 per cent error
Wilson method with 5,000 ohm resistors = 2.44 per cent error
Goldberger method = 8.35 per cent error.

TECHNIQUE

In the registering of unipolar extremity leads with the Wilson central terminal, the exploring wire is commonly attached to the limb electrode which is part of the central terminal circuit. That is, if Lead V_L is desired, the exploring wire is connected to Electrode B of Fig. 5. *This procedure is incorrect and may introduce very serious error in the electrocardiogram.* The correct way to connect the patient is shown in Fig. 5. Instead of connecting the exploring wire

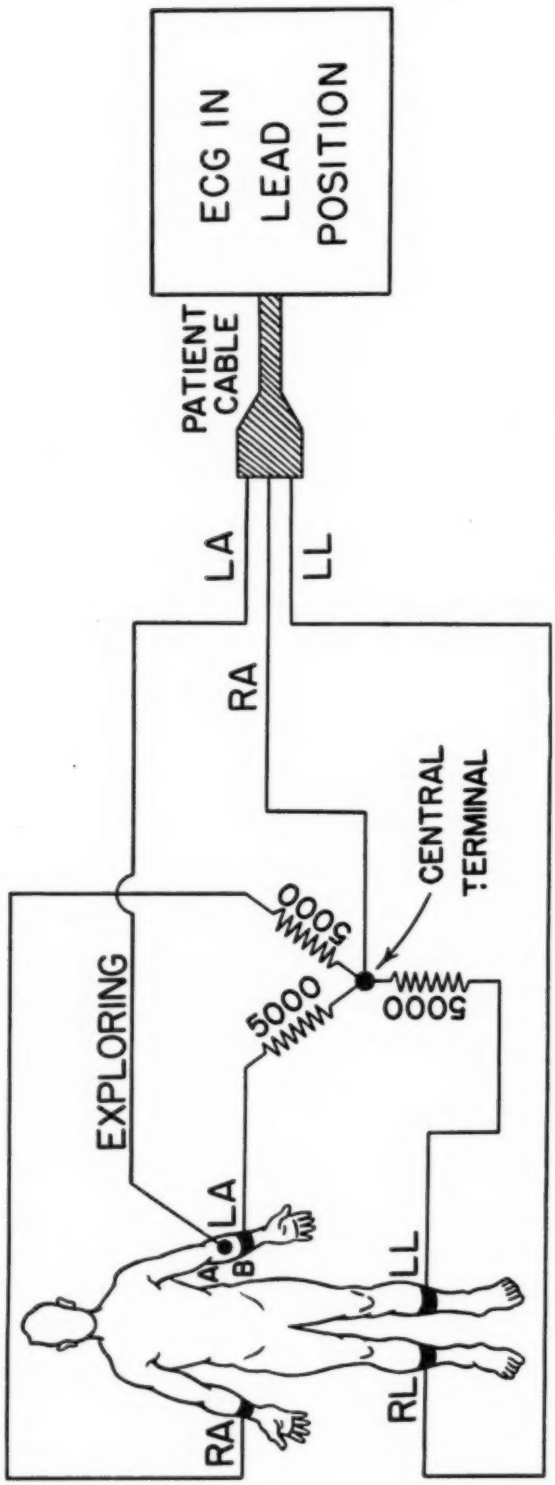


Fig. 5.—Connections for unipolar extremity leads by the Wilson technique.

to Electrode B when registering Lead V_L, another electrode A must be used and the exploring wire attached to it. The spacing between Electrodes A and B is unimportant, but electrode jelly must not be allowed to communicate between the two electrodes. The connection to the right leg is useful for eliminating alternating current interference because several makes of electrocardiographs require that the patient be grounded to the apparatus. In these electrocardiographs the unused limb, such as the left leg in Lead I, the left arm in Lead II, and the right arm in Lead III, is grounded to the apparatus via the lead selector switch. When the Wilson central terminal circuit is employed, the right arm, left arm, and left leg are not available for grounding. The right leg is, therefore, the most convenient portion of the patient to ground.

The magnitude of error that is introduced in the unipolar extremity lead electrocardiograms if the exploring electrode is connected to Electrode B of Fig. 5 may be calculated. Fig. 6 is a circuit which is equivalent to the one shown in Fig. 5 but takes into consideration the skin resistance under all electrodes. As before, let

R_{RA} = resistance of skin under right arm electrode = 1,000 ohms
R_{LA} = resistance of skin under left arm electrode = 2,000 ohms
R_{LL} = resistance of skin under left leg electrode = 3,000 ohms
R_E = skin resistance under Electrode A.

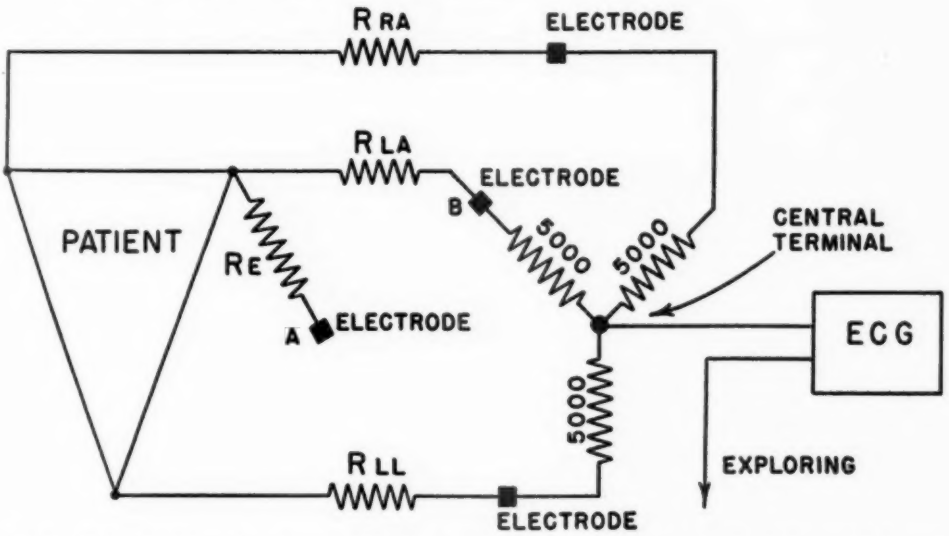


Fig. 6.—Equivalent electrical circuit of Fig. 5 in which the skin resistance under the right arm, left arm, and left leg electrodes are taken into consideration.

If Lead V_L is taken by the method shown in Fig. 5, the action potentials registered by the electrocardiograph of Fig. 6 are formed between the central terminal and Electrode A. This is the actual V_L lead because the effects of R_E are negligible when an electronic electrocardiograph is used,[19] and in a string electrocardiograph the string sensitivity is adjusted to compensate for the effects of resistance in series with it. However, if the exploring wire is placed on

Electrode B of Fig. 5, then Lead V_L is registered between the central terminal of Fig. 6 and Electrode B. If R_{LA} is 2,000 ohms, then Lead V_L is registered with an amplitude equal to five-sevenths the actual value because of the division of the action potential between R_{LA} and the 5,000 ohm resistor. Obviously, the higher the skin resistance under the electrode, the greater is the magnitude of error.

If the Goldberger central terminal were used with the incorrect technique, zero action potential or an isoelectric line would be registered by the electrocardiograph. The correct connections with the Goldberger central terminal are as with the Wilson central terminal.

A natural question which should be considered at this time is the relative accuracies of the Einthoven string galvanometer electrocardiograph and the electronic electrocardiograph when used in conjunction with the Wilson and Goldberger central terminals. When Wilson first described the central terminal, he suggested that a stage of electronic coupling be interposed between the central terminal-patient circuit and the string.

As previously mentioned, any resistance which is placed in series with a string requires a slackening of the string tension. *In a string galvanometer, the galvanometric speed is proportional to the square root of the tension and the tension is proportional to the reciprocal of the sum of the string resistance and any resistance in series with it.* For example, the usual resistance of a string is approximately 2,000 ohms and a well-scrubbed normal patient may attain a resistance of approximately 2,000 ohms which totals 4,000 ohms. Let us assume that the minimum galvanometer speed of the string electrocardiograph under such operating conditions is 0.01 second. Should the patient resistance increase to, say, 6,000 ohms, then the total resistance of the circuit becomes 8,000 ohms. In turn, the string must be slackened so that the new galvanometric speed is reduced to 0.014 second. Lewis and Gilder[18] have shown that galvanometric speeds slower than 0.02 second will produce sluggish and inaccurate electrocardiograms in human beings.

Fig. 7 is the basic circuit of the Wilson central terminal connected to a string galvanometer and patient. As before, the maximum allowable resistance in the circuit so that the galvanometric speed will not be slower than 0.02 second is

$$\frac{0.01}{\sqrt{4000}} = \frac{0.02}{\sqrt{R}}$$

or $$R = 16{,}000 \text{ ohms}$$

If we subtract the 2,000 ohm string resistance, then 14,000 ohms is allowable for the rest of the circuit resistance. Let us assume that

$$R_E = R_{RA} = R_{LA} = R_{LL}$$

This may be done because the internal resistance of a patient is small compared with the contact resistance. Then

$$\frac{R_E + 5000}{3} + R_E = 14{,}000$$

or $$R_E = 9{,}250 \text{ ohms}$$

This means that if the contact resistances at the right arm, left arm, and left leg and exploring electrodes do not exceed approximately 9,000 ohms, the galvanometric speed will not be slower than 0.02 second. In practice, such values of resistance are rarely exceeded; therefore, the string electrocardiograph should record clinically accurate unipolar electrocardiograms on human beings from a galvanometric speed standpoint.

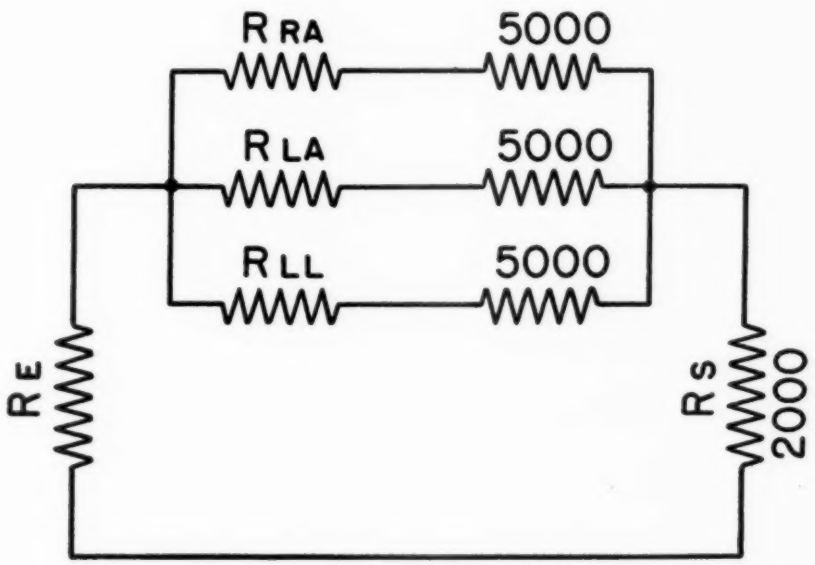


Fig. 7.—Basic circuit of the Wilson central terminal connected to a string galvanometer and patient in which:

R_{RA} = skin resistance under right arm electrode
R_{LA} = skin resistance under left arm electrode
R_{LL} = skin resistance under left leg electrode
R_S = string resistance = 2,000 ohms
R_E = skin resistance under exploring electrode plus internal resistance of patient

Galvanometric speed versus patient resistance is of no consequence in electronic electrocardiographs or when a stage of electronic coupling is used with the Einthoven string galvanometer.[1,2,17]

DISCUSSION

Wolferth and Livezey[5] have differed with Wilson and associates[12] as to the accuracy of the central terminal method for registering unipolar electrocardiograms. They are agreed, however, that an accurate method for registering unipolar electrocardiographic leads would be a most important electrocardiographic method. Wolferth and Livezey state: "It is of vital importance to electrocardiography that if error in matters of this nature exist, such error be recognized. If, on the other hand, there is no important source of error in Wilson's 'unipolar' leads, they should be used for practically all electrocardiographic work."

When Wilson and associates devised the central terminal, they suggested that its accuracy is dependent upon the validity of the equilateral triangle theory and Kirchhoff's laws of electric networks. They claimed that the potential which exists at the central terminal must be equal at every instant to the mean of the potentials at the electrodes on the right arm, left arm, and left leg. Also, if the equilateral triangle theory is 100 per cent valid, the sum of the potentials at the three limbs must total zero and thus the central terminal potential must be equal to zero. Our mathematical analysis shows, however, that the potential at the central terminal may be modified by dissimilar patient resistance in each of the three limbs. Differences in resistance at the three limbs is caused by unlike electrical conductivity of the skin under each of the three extremity electrodes.

Almost everyone is agreed that the equilateral triangle theory of Einthoven, Fahr, and De Waart is not 100 per cent correct. The controversial point is as to the amount of error that may be present. Wilson and his associates state: "In our opinion, there is no reason to suppose either that Einthoven and his associates had any false notions as to the general character of the heart's electrical field or that they considered their method of determining the position of the electrical axis of the heart entirely free of error. In 1921, a paper by Lewis, Drury, and Iliescu[18] on the electrical axis of the auricle in clinical cases of auricular flutter raised a question as to the conditions under which the principles of Einthoven's triangle are applicable. A letter to Einthoven concerning the matter was answered by him on November 21, 1921 as follows:

" 'In regard to the equilateral triangle I fully agree with you. I assumed in my original paper "Ueber die Richtung and die Manifeste Grösse der Potential—schwankungen etc.," in the center of the triangle a "bipole," that is to say, two points lying very close together and showing a potential difference. The triangle was supposed to be a homogenous sheet of conducting material and in regard to the distance between the two points of the bipole, of a large, let us say infinite extent.

" 'The applicability of this scheme to the ordinary leads of the human body depends indeed on the fact that the electrodes are at a relatively great distance from the heart. If they are placed near the heart the errors are greater and the more so the closer they get to the heart. Even in the case of the ordinary leads from the limbs the results cannot be absolutely exact.' "

Several independent investigators[7,8,9,10] who have performed experiments on the cadaver to determine the validity of the equilateral triangle are agreed that the direction and relative magnitude of deflections in the limb leads are within close limits of the relationships expressed in the equilateral triangle theory. Others[11,12,13] have compared the central terminal of the Einthoven, Fahr, and De Waart triangle with other central terminals, each connected to a set of three electrodes located equidistant from the heart and lying at the apices of a triangle enclosing it. All but Wilson and his associates observed that the potential differences between the various central terminals were very close to zero. Wilson and co-workers found that the differences in potential did not exceed 0.15 millivolt. The immersion experiments[12,15,16] showed a greater degree of discrepancy. The

experiments of Wolferth and Livezey, in which they paired an exploring electrode with one placed over the spine of the right scapula and compared it to the Wilson central terminal method, show considerable discrepancy.

Nowhere in the literature which pertains to the validity of the equilateral triangle theory has anyone shown that serious error may have been present in the experiments performed by Fahr and Weber, by Wagner, and by Johnston, Kossmann, and Wilson on cadavers and those of Wilson and Herrmann on the living dog. Until concrete proof is produced that the cardiac action potentials at the limbs deviate a considerable amount from the relationships expressed in the equilateral triangle theory, it is our contention that we are not too far wrong in assuming that a reasonably good similarity exists. That is, experimental data indicate that the deviations of the action potentials at the limbs from values indicated in the equilateral triangle theory are small enough to warrant clinical application of the theory.

By mathematical procedure it can be proved that the principles fundamental to the central terminal circuit are correct for unipolar electrocardiographic applications. This holds true only when the patient resistances in the three limbs are identical. Any dissimilarity of resistance at the three extremities modifies the central terminal potential and, in turn, the unipolar electrocardiogram.

TABLE I. EFFECTS OF DISSIMILAR LIMB RESISTANCE ON V_R LEAD IN A HYPOTHETICAL CASE

METHOD	RA PATIENT RESISTANCE (OHMS)	LA PATIENT RESISTANCE (OHMS)	LL PATIENT RESISTANCE (OHMS)	C. T. POTENTIAL (MILLIVOLTS)	ERROR IN V_R LEAD (PER CENT)
Theoretical	1,000	2,000	3,000	0	0
10,000 ohm Wilson	1,000	2,000	3,000	−0.043	3.59
5,000 ohm Wilson	1,000	2,000	3,000	−0.077	6.42
Goldberger	1,000	2,000	3,000	−0.355	29.5

In Table I are shown the results of our calculations on a hypothetical case when the patient resistance in the right arm due to skin resistance is 1,000 ohms, in the left arm, 2,000 ohms, and in the left leg, 3,000 ohms. In clinical electrocardiography, it is not unusual to obtain even larger resistance differentials at the limbs.[21] Note how the central terminal potential deviates from the theoretically correct value by the use of the Wilson and Goldberger techniques. Obviously, *the higher the value of the three fixed resistors, the less is the deviation of the central terminal voltage from zero.* Because the central terminal voltage deviates from zero, the error present in the Wilson circuit with 10,000 ohm resistors is 3.59 per cent, and when 5,000 ohm resistors are employed the error is increased to 6.42 per cent; but when the Goldberger technique is employed, the error jumps to 29.5 per cent. In clinical electrocardiography an error of 6.42 per cent may not be too serious, but 29.5 per cent is enormous. *Similarly, the magnitude of*

error in unipolar chest leads due to the deviation of the central terminal voltage would be of the same order of magnitude.

Dissimilar patient resistance in the limbs does not produce as much error in the augmented unipolar extremity leads as occurs in the unipolar extremity leads and in the unipolar chest leads. In Table II are shown our calculated errors in the aV_R lead by the Wilson and Goldberger techniques. It so happens that the left arm patient resistance in this case was 2,000 ohms and the left leg was 3,000 ohms. However, more error would be present if the left arm resistance were 1,000 ohms and the left leg resistance unchanged. Such a resistance combination occurs in the aV_L lead on this hypothetical patient. For comparison purposes we merely interchange the limb resistances and calculate the new value of aV_R error which is given in Table III. Under the more severe condition of limb resistance represented in Table III, the error in the Goldberger method is 8.38 per cent, as compared to 2.44 per cent when the Wilson method with 5,000 ohm fixed resistors is used and 1.28 per cent with 10,000 ohm fixed resistors.

TABLE II. EFFECTS OF DISSIMILAR LIMB RESISTANCE ON aV_R LEAD IN A HYPOTHETICAL CASE

METHOD	LA PATIENT RESISTANCE (OHMS)	LL PATIENT RESISTANCE (OHMS)	ERROR IN aV_R LEAD (PER CENT)
Theoretical	2,000	3,000	0
10,000 ohm Wilson	2,000	3,000	0.67
5,000 ohm Wilson	2,000	3,000	1.1
Goldberger	2,000	3,000	3.3

TABLE III. EFFECTS OF DISSIMILAR LIMB RESISTANCE ON aV_R LEAD IN A HYPOTHETICAL CASE

METHOD	LA PATIENT RESISTANCE (OHMS)	LL PATIENT RESISTANCE (OHMS)	ERROR IN aV_R LEAD (PER CENT)
Theoretical	1,000	3,000	0
10,000 ohm Wilson	1,000	3,000	1.28
5,000 ohm Wilson	1,000	3,000	2.44
Goldberger	1,000	3,000	8.35

By similar mathematical procedure, the magnitude of error present in augmented extremity leads and unipolar chest and limb leads for various combinations of skin resistance in the three limbs may be calculated. This would be a rather lengthy procedure and is beyond the scope of this paper.

By mathematical approach we have shown that the higher the resistances in the central terminal circuit, the less is the error that may be introduced by

dissimilar contact resistance at the limbs. Wilson appreciated this fact when he first used 25,000 ohms but discarded this value in favor of 5,000 ohms because of alternating current interference. By more modern electrical techniques, central terminal resistances of 200,000 ohms may be used with a negligible increase of interference pick-up. This is especially important when registering simultaneous unipolar leads or unipolar leads in conjunction with bipolar leads. The simultaneous registration of unipolar leads has been neglected and is much needed for a better understanding of the mechanism of production of these leads.

CONCLUSIONS

1. The experiments of Fahr and Weber, of Wagner, and of Johnston, Kossmann, and Wilson on cadavers and those of Wilson and Herrmann on the living dog show that the cardiac action potentials at the right arm, left arm, and left leg are a very close approximation of the values expressed in the equilateral triangle theory of Einthoven, Fahr, and De Waart. To our knowledge, nowhere in the literature has anyone shown that serious error may have been present in these experiments. It is our contention, therefore, that we cannot be too far wrong in assuming that the deviation of the action potentials at the limbs from the values indicated in the equilateral triangle theory are small enough to warrant clinical application.

2. When Wilson, Macleod, and Barker suggested the central terminal method for registering unipolar electrocardiograms, they stated that the accuracy of the method is dependent upon the validity of the equilateral triangle theory and Kirchhoff's laws of electric networks. We have found that dissimilarity of skin resistance under the extremity electrodes which comprise the central terminal are an important additional factor.

3. It may be shown by mathematical approach that the potential at the Wilson or Goldberger central terminal is zero *only* under the following conditions:

A. If the equilateral triangle theory is 100 per cent correct.

B. If the skin resistances under the extremity electrodes which comprise the central terminal circuit are identical in value.

4. If the voltages at the limbs deviate a slight amount from the values expressed in the equilateral triangle theory, the central terminal potential is slightly removed from zero and the unipolar electrocardiogram is modified slightly.

5. Dissimilarity of skin resistance under the three extremity electrodes is unavoidable in clinical electrocardiography. The use of fixed resistors as suggested by Wilson, Macleod, and Barker minimizes the degree of error. The Goldberger central terminal does not employ the three fixed resistors but depends upon the skin resistance only. Therefore, additional error may be introduced when the Goldberger technique is used for registering unipolar electrocardiograms.

6. The Wilson central terminal may be used for registering augmented unipolar extremity leads. The basic principle is exactly the same as that suggested by Goldberger.

7. Dissimilar skin resistance under the extremity electrodes which comprise the augmented central terminal does not introduce as much error in the augmented unipolar extremity leads as occurs in unipolar extremity leads and unipolar chest leads.

8. Error in the augmented unipolar extremity leads due to dissimilar skin resistance under the extremity electrodes is less with the Wilson central terminal than with the Goldberger technique.

9. If the Wilson central terminal is used for registering unipolar extremity leads, the exploring wire must be applied to an electrode other than the one which forms the central terminal. The separation between the two electrodes is unimportant. Electrode paste must not communicate between the electrodes. If the Goldberger central terminal is used, the procedure is the same. Application of the exploring wire to the electrode which forms the Goldberger central terminal will register an isoelectric line, whereas the Wilson central terminal will register an augmented unipolar extremity lead which is reduced in magnitude.

10. If precaution is used in the scrubbing of the patient, the Wilson 5,000 ohm central terminal, operating in conjunction with an Einthoven string electrocardiograph, will register reasonably accurate unipolar leads.

11. Error may be introduced in unipolar electrocardiographic leads if the Goldberger central terminal is used. As far as we can see, there are no obvious advantages in eliminating the fixed resistors which make up the central terminal. The technique for registering augmented unipolar extremity leads suggested by Goldberger has definite merit, but better results are obtained theoretically if Goldberger's technique is used with the Wilson central terminal.

REFERENCES

1. Wilson, F. N., Macleod, A. G., and Barker, P. S.: Electrocardiographic Leads Which Record Potential Variations Produced by the Heart Beat at a Single Point, Proc. Soc. Exper. Biol. & Med. **29**:1006, 1932.
2. Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Electrocardiograms That Represent the Potential Variations of a Single Electrode, Am. Heart J. **9**:447, 1934.
3. Einthoven, W., Fahr, G., and de Waart, A.: Ueber die Richtung und die manifeste Grösse der Potentialschwankungen im menschlichen Herzen und ueber den Einfluss der Herzlage auf die Form des Elektrokardiogramms, Arch. f. d. ges. Physiol. **150**:308, 1913.
4. Kirchhoff, G.: Gesammelte Abhandlungen, Leipzig, 1882, Johann Ambrosius Barth, p. 15.
5. Wolferth, C. C., and Livezey, M. M.: A Study of Methods of Making So-Called Unipolar Electrocardiograms, Am. Heart J. **27**:764, 1946.
6. Lewis, T., Drury, A. N., and Iliescu, C. C.: A Demonstration of Circus Movement in Clinical Flutter of the Auricles, Heart **8**:341, 1921.
7. Fahr, G., and Weber, A.: Ueber die Ortsbestimmung der Erregung im Menschlichen Herzen mit Hilfe der Elektrokardiographie, Deutsches Arch. f. klin. Med. **117**:361, 1914.
8. Wagner, G.: Physikalische Untersuchungen Zum Dreischkschema nach. Einthoven, Zentralbl. f. Herz-u. Gefässkr. **16**:1, 1924.
9. Johnston, F. D., Kossmann, C. E., and Wilson, F. N.: Unpublished observations discussed *in*: Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., and Barker, P. S.: On Einthoven's Triangle, the Theory of Unipolar Electrocardiographic Leads, and the Interpretation of the Precordial Electrocardiogram, Am. Heart J. **32**:277, 1946.
10. Wilson, F. N., and Herrmann, G. R.: Unpublished observations discussed *in*: Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., and Barker, P. S.: On Einthoven's Triangle, the Theory of Unipolar Electrocardiographic Leads, and the Interpretation of the Precordial Electrocardiogram, Am. Heart J. **32**:277, 1946.

11. Burger, R., and Wuhrmann, F.: Ueber das Elektrische Feld des Herzens. II. Mitteilung, Cardiologia **3**:139, 1939.
12. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., and Barker, P. S.: On Einthoven's Triangle, the Theory of Unipolar Electrocardiographic Leads, and the Interpretation of the Precordial Electrocardiogram, AM. HEART J. **32**:277, 1946.
13. Arrighi, F.: El Eje Electrico del Corazon en el Espacio, Facultad de Ciencias Medicas, Univ. Nacional de Buenos Aires, Buenos Aires, 1938.
14. Goldberger, E.: A Simple, Indifferent, Electrocardiographic Electrode of Zero Potential and a Technique of Obtaining Augmented, Unipolar, Extremity Leads, AM. HEART J. **23**:483, 1942.
15. Eckey, P., and Frölich, R.: Zur Frage der unipolaren Ableitung des Elektrokardiogramms, Arch. f. Kreislaufforsch. **206**:181, 1938.
16. Burger, R.: Ueber das Elektrische Feld des Herzens. I. Mitteilung, Cardiologia **3**:56, 1939.
17. Rappaport, M. B., and Rappaport, I.: Electrocardiographic Considerations in Small Animal Investigations, AM. HEART J. **26**:662, 1943.
18. Lewis, T., and Gilder, M. D.: The Human Electrocardiogram; a Preliminary Investigation of Young Male Adults, to Form a Basis for Pathological Study, Phil. Tr. Roy. Soc. **202** (B): 351, 1912.
19. Wilson, F. N.: Personal communication.
20. Bryant, J. M., and Johnston, F. D.: Errors Encountered in the Use of the Goldberger Central Terminal, J. Clin. Investigation **25**:919, 1946.
21. Rappaport, M. V., and Williams, C.: Unpublished data.

TRANSIENT VENTRICULAR FIBRILLATION

II. The Effects of Gradually Induced Oxygen Deficiency on Patients With Transient Ventricular Fibrillation and on Patients With Periodic Standstill of the Ventricle

Sidney P. Schwartz, M.D., George C. Leiner, M.D., and R. J. Michtom, M.D.*
New York, N. Y.

THE purpose of this study was to determine the effects of gradually induced oxygen deficiency on patients subject to transient seizures of ventricular fibrillation. The alterations in the rhythm of the heart following anoxemia in such patients were compared with the changes in the cardiac mechanism of patients with auriculoventricular dissociation subject to recurrent attacks of standstill of the ventricles. Since the immediate factors that initiate transient seizures of ventricular fibrillation are still unknown, it was hoped that these experiments would yield some data on the coefficients responsible for this unusual mechanism in man.

REVIEW OF LITERATURE

Experimental Observations.—It is well established from experimental observations that in the resting animal the earliest effects of anoxia on the heart result in an acceleration of the sinus rate.[1,2] Wiggers[3] has recently pointed out that a progressive decrease in the respired oxygen volumes to about 12 per cent (which period he calls *hypoxia* and which corresponds to arterial blood oxygen saturation of about 75 per cent) always increases the flow of blood by redistribution of blood flow and by cardiac acceleration. He attributes the increased cardiac rate to a decreased vagal tone, and perhaps to some direct effect on the sinoauricular node. When the oxygen in the inspired air falls below 12 per cent (which he calls the "true period of anoxia"), a greater stroke volume occurs, there is a further increase in the velocity of ejection, and the economy of effort is enhanced. When the oxygen declines to 7 or 6 per cent, which corresponds to an oxygen saturation of the arterial blood between 50 and 35 per cent, a coronary crisis occurs. The arterial pressure declines abruptly, the pulse pressure is reduced, the systolic pressure decreases, the venous pressure rises greatly, and various types of *conduction and rhythm* disturbances may occur.

From the Medical and Pulmonary Divisions of the Montefiore Hospital for Chronic Diseases, New York City.

*Assistant Resident in Medicine.

The delayed conduction of the normal cardiac impulse with progressively developing A-V dissociation has been attributed to the direct effect of the asphyxial state upon the A-V mechanism of the heart.[4,5] It was found to be independent of the action of the vagus nerves, for it occurred in the atropinized animal as well as after section of the vagi.[6,7] In this state of anoxemia, the sinoauricular node of the mammalian heart was found to be as sensitive as the bundle of His.

Resnik[8] also observed a predisposition of the auricles to fibrillate when these chambers of the heart were stimulated by a direct current in the presence of anoxia. He pointed out that a damaged heart, when subjected to anoxemia, may exhibit early a functional disturbance which will appear only in the presence of a more profound anoxemia in the normal heart. Both Resnik[8] and Criep[9] noted a definite tendency of the *ventricles to fibrillate* after the establishment of the various grades of block that appeared in the advanced stages of oxygen want. In Criep's studies, ectopic ventricular beats preceded ventricular fibrillation in the presence of both auricular and ventricular standstill, while auricular fibrillation appeared as an early manifestation. These profound alterations in the rhythm of the heart were found not only after the animal was deprived of an adequate amount of oxygen, but also in the course of anaphylactic reactions that ended in death.

Clinical Observations.—There are ample correlated observations on the effects of gradually induced oxygen want on the RS-T segments and the T waves of the electrocardiograms of individuals with normal hearts as well as on patients with angina pectoris, coronary insufficiency, and myocardial disease.[10,14] In the majority of effective responses to this form of anoxia, the electrocardiograms reveal a lowering of the RS-T segment below the isoelectric line and eventually a final negativity of T waves. However, there is only a single study in the literature in which abnormal rhythms of the heart were emphasized as a finding during "extreme" oxygen want.

In studying the response of the circulation in men to gradually reduced oxygen tension, Greene and Gilbert[15] observed an acceleration of the sinus rate during the earliest phases of oxygen reduction. This was usually followed by a marked sinus arrhythmia with a decrease in the amplitude of the main ventricular deflections and the size of the T waves. A slowing of the sinus rate followed this acceleration, in which the rate was lowered from an average of 110 beats per minute to 80 beats before there appeared the various grades of A-V conduction disturbances leading to partial and complete heart block. Occasionally there was standstill of the auricles. A drop in blood pressure observed at this stage of anoxemia was found to be independent of the changes in the rate and rhythm of the heart. Note should be made here that in four normal individuals the appearance of these far-advanced abnormal rhythms coincided with loss of mental attention, appearance of cyanosis, changes in respiration, loss of voluntary control, and, finally, loss of consciousness. All of these signs were transitory and disappeared immediately when the mask was removed.

METHOD OF STUDY

Two patients who were experiencing transient seizures of ventricular fibrillation and two patients with periodic standstill of the ventricles form the subjects of this study. In one patient recurring attacks of transient ventricular fibrillation appeared after the development of transient periods of A-V dissociation in the course of a normal sinus mechanism. The other three patients had established A-V dissociation.

These experiments were carried out at a time when it was certain that the patients had not had any changes in their cardiac mechanism for at least forty-eight hours. It was definitely determined from both a study of the heart and pulse rates, while the patients were connected to the electrocardiographic circuit, that the basic ventricular rate was fairly constant prior to the onset of the experiments, that is, that it did not vary more than five beats per minute. Two patients were in bed constantly and two were ambulatory. No drugs were administered for at least one week prior to these studies. All four patients had mild signs of congestive heart failure with shortness of breath and three had cyanosis of the lips and nail beds.

One method of rebreathing was identical to that used by others in similar experiments.[15] The subject was placed in a reclining position and connected to a basal metabolism machine filled with room air and the carbon dioxide was removed by soda lime. Another method consisted of having the subject rebreathe in a small canvas bag filled with room air without the removal of the carbon dioxide. Continuous electrocardiograms were recorded prior to, during, and subsequent to the rebreathing periods.

The experiments were terminated when such signs were observed as loss of mental attention and sustained voluntary control, intense cyanosis, or abnormal changes in the type of breathing.

RESULTS

The Effects of Anoxemia on Patients With Transient Ventricular Fibrillation.—One woman showed a sinus rhythm and developed transient seizures of ventricular fibrillation after the onset of A-V dissociation. Rebreathing for only four minutes and thirty-seven seconds changed her sinus mechanism to one of heart block with the auricles beating 78 per minute and the ventricles 32. This type of A-V dissociation persisted after the termination of the experiment for several days before there was a return to the sinus mechanism. It is of interest to note that the heart block could also be readily induced in this patient by the intramuscular injection of epinephrine hydrochloride[16] as well as by the intravenous injection of digitalis bodies.[17]

In this woman and in another patient the effects of rebreathing were variable when the A-V dissociation had already been established. In the first case, rebreathing either in the basal metabolism machine or in the bag yielded no change in the cardiac rhythm except a slight acceleration of the auricles at the end of seventeen minutes when the experiment had to be discontinued because of discomfort. The ventricular rate remained unchanged.

In the other patient rebreathing was followed in the first four minutes by an acceleration of the basic auricular rate from 88.3 beats per minute to 100 beats. The ventricular rate in the meantime increased to 32.6 beats from a previous average of 30.7 beats (Fig. 1,*A* and *B*). At seven and nine minutes, respectively,

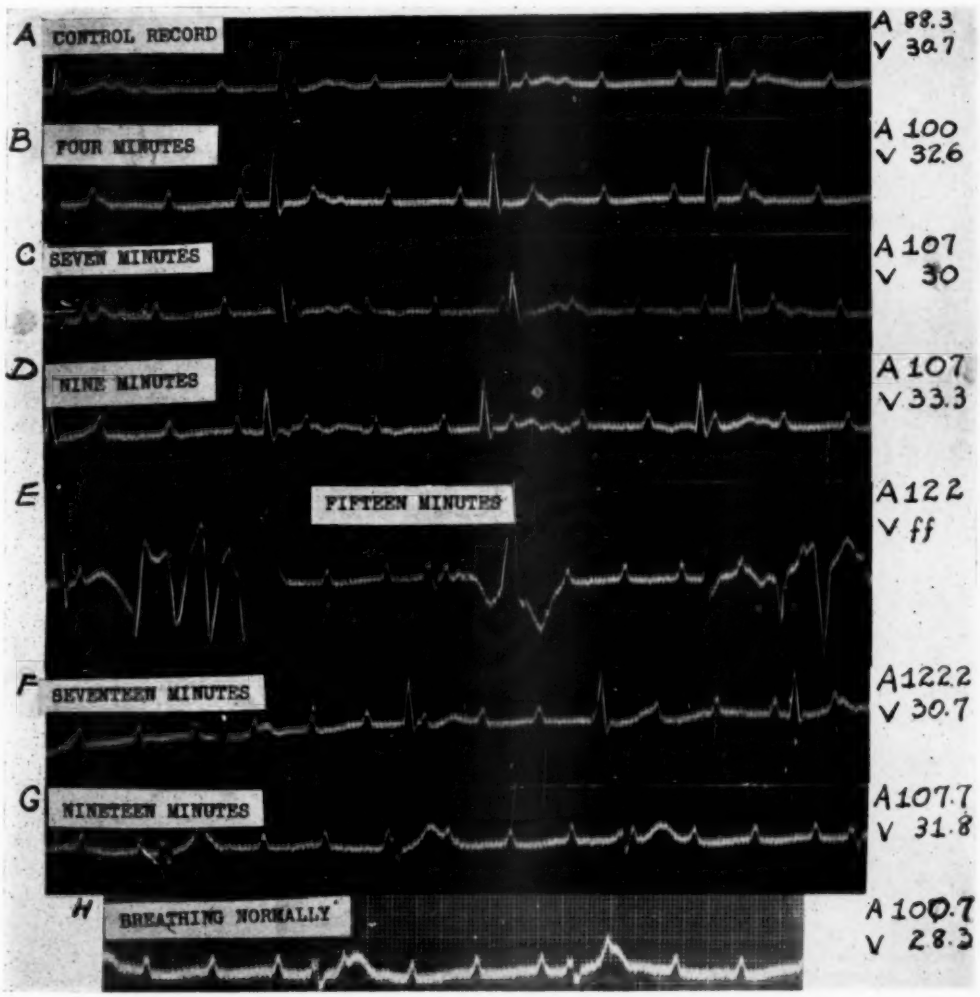


Fig. 1.—The successive alterations in the cardiac mechanism following rebreathing in a patient with A-V dissociation subject to transient seizures of ventricular fibrillation. Note the progressive increase in the auricular rate and the development of a short run of ventricular fibrillation, fifteen minutes after rebreathing (*E*).

after rebreathing, the auricles beat at the rate of 107 per minute and the ventricles increased to 30 beats (Fig. 1,*C* and *D*). Fifteen minutes after rebreathing, the auricular rate suddenly increased to 122.2 beats per minute and the basic ventricular rate was interrupted at first by single and then by alternate premature beats of the ventricles and finally by large aberrant ventricular oscillations that

resembled in every respect the prefibrillatory period observed in this patient prior to the onset of syncopal attacks due to transient ventricular fibrillation.[18] The basic ventricular complexes were also aberrant, as compared with the deflections present before the onset of the experiment. Two minutes after the removal of the mask, the auricular rate was still 122.2 beats per minute, but the ventricular rate now averaged 30.7 beats and the rhythm was perfectly regular (Fig. 1,*F*). The ventricular complexes now resumed their original size and form. However, within two minutes, that is, nineteen minutes after the onset of the experiment, they changed shape again and became aberrant, even though the patient was breathing room air. The auricles then slowed to 100.7 beats and remained at this rate with a regular rhythm although the ventricles were now beating at only 28.3 beats (Fig. 1,*H*). This type of cardiac mechanism persisted for several hours when finally there was a return to the same rate and rhythm that was present at the beginning of the experiment.

Throughout the entire period of observation this patient did not lose consciousness and his only complaint was a slight precordial pain that set in with the appearance of the ventricular irregularities. The pain disappeared when the mask was removed.

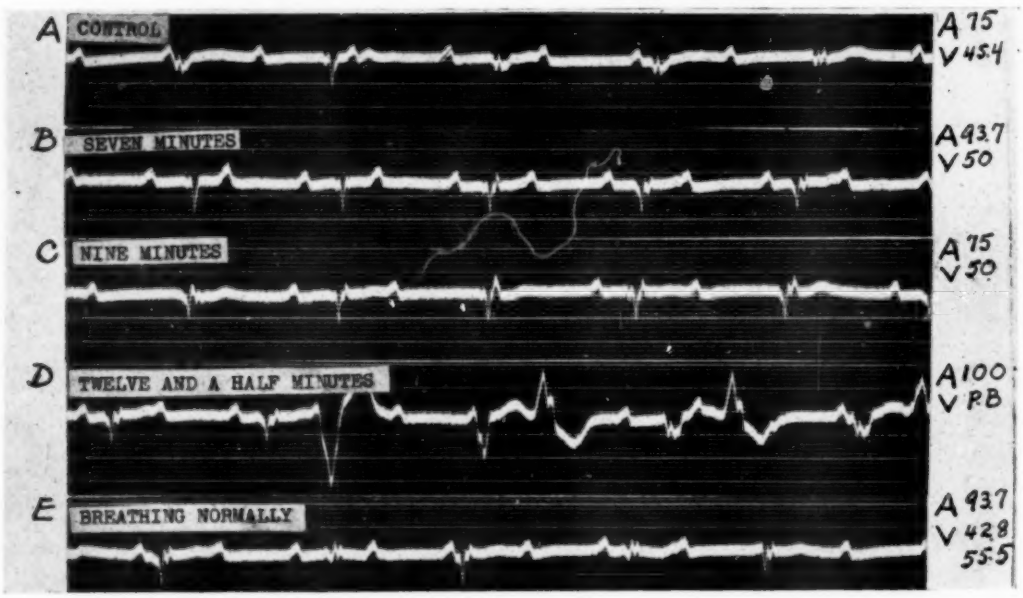


Fig. 2.—The successive alterations in the cardiac mechanism following rebreathing in a patient with A-V dissociation subject to periodic standstill of the ventricles. Note the increase in the auricular and ventricular rates and the development of premature beats of the ventricles (*D*).

The Effects of Anoxia on Patients With Periodic Standstill of the Ventricles.—In an ambulatory patient with periodic standstill of the ventricles in the course of established A-V dissociation, rebreathing for seven minutes in the basal metabolism machine increased the basic auricular rate from 75 beats per minute to 93.7 (Fig. 2,*A* and *B*). The basic ventricular rate was accelerated from 45 to

50 beats per minute. There was no essential change in the shape, size, or form of the basic ventricular deflections, which were of two distinct types, in the intervals when the patient was free from periodic standstill of the ventricles.

After nine minutes of rebreathing, the auricular rate slowed to 75 beats per minute (Fig. 2,*C*) and increased again within three and one-half minutes to 100.7 beats. Now the basic ventricular rhythm was interrupted by alternate premature beats of the ventricles and there was an increase in the width of the basic ventricular complexes which became markedly aberrant, as compared with previous deflections of the ventricles (Fig. 2,*D*). At this time the patient complained of pains in his chest, but he was not conscious of any change in his heart rhythm. His breathing was accelerated; there was a general increase in his cyanosis; and he asked to have his mask removed.

Immediately the premature beats of the ventricles and the aberrant ventricular complexes disappeared abruptly. However, for the next few minutes there set in a peculiar irregularity of the ventricles in the presence of a regular auricular rhythm with the auricles beating at 93.7 beats per minute. The ventricular rate varied from 42.8 to 55 beats per minute. A coupled rhythm was present in which the alternate sphygmic intervals between the basic ventricular complexes were equal to each other (Fig. 2,*E*). The ventricular deflections were variable in shape and size from beat to beat. This type of abnormal irregularity persisted for seventeen minutes before there was a return to the basic rate and rhythm which was present before the beginning of the experiment.

In another patient with periodic standstill of the ventricles, rebreathing room air in a bag for sixteen minutes on one occasion and thirteen minutes on another, without the elimination of carbon dioxide by soda lime, resulted in a transient acceleration followed by a temporary slowing of the auricular rate, but there was no change in the rate or rhythm of the ventricles, which did not vary more than three beats per minute throughout the experiment.

DISCUSSION

These observations reveal that patients who are subject to transient seizures of ventricular fibrillation easily develop A-V dissociation when anoxia is induced in them by the rebreathing method in the presence of normal sinus rhythm. After the appearance of either transient or permanent A-V dissociation, progressively increasing oxygen want results in the development of short, recurring, and widely aberrant ventricular oscillations, which in their final analysis are short runs of ventricular fibrillation. In the patients observed in this study, these profound alterations in the rhythm of the heart appeared much earlier in the course of oxygen want than they did in normal individuals.[15] This is likely due to the fact that these patients already had signs of mild congestive heart failure when the experiments were begun. It is known that congestive heart failure is accompanied by a lowered arterial and venous concentration of oxygen.[19,20] Peters and Barr[21] have observed changes in the dissociation curve for carbon dioxide and in hydrogen ion concentration of the blood in advanced heart failure, and Siebeck[22] noted unequal pulmonary expansion in cardiac insufficiency resulting in an imperfect mixture of gases in the lungs.

That progressive oxygen want is directly responsible for these abnormal ventricular irregularities may be gained from the simultaneous effects produced on the rate and rhythm of the auricles. There is at first an acceleration of the auricular rate and then at times there follows a transitory slowing. Occasionally, with increased anoxemia, there is a progressive acceleration of the auricles. This may be present for some time after rebreathing is stopped. The behavior of the auricular rate and rhythm during A-V dissociation is identical with that observed in anoxic experiments on individuals with normal sinus rhythm. It indicates that the changes in ventricular rate and rhythm must be due to the same operating factor, that is, reduced oxygen tension, and not to fortuitous circumstances.

In comparison with these changes, it was noted that in patients in whom standstill of the ventricles was responsible for recurring syncopal attacks, rebreathing initiated only isolated premature beats of the ventricles, at times in the form of a bigeminal rhythm. Occasionally anoxemia influenced the A-V pacemaker so as to accelerate the ventricular rate irregularly.

These arrhythmias of the ventricles following anoxemia suggest the possibility of using the rebreathing method for making a differential diagnosis of the underlying cardiac mechanism responsible for syncopal attacks in patients with A-V dissociation. In patients in whom standstill of the ventricles is the cause of syncopal attacks, rebreathing should result in the appearance of only isolated premature beats of the ventricles. In patients in whom transient ventricular fibrillation is the underlying cardiac rhythm, rebreathing should result in the appearance of short runs of ventricular fibrillation.

Unfortunately, these experiments reveal a marked inconstancy in the response of the diseased human heart to progressively increasing oxygen want. In the same patient on some occasions rebreathing for only a very short period (four minutes) yielded profound disturbances in rhythm, whereas at other times longer periods of rebreathing (nineteen minutes) resulted in no changes at all. Furthermore, the presence of anginal pains following these tests and the general discomfort that rebreathing entails in an already breathless patient, makes this method an impractical test for this type of differential diagnosis.

It is of some interest to speculate on the reasons why only those patients who are subject to transient seizures of ventricular fibrillation should respond to anoxemia with the appearance of a prefibrillatory period and ventricular fibrillation. It certainly cannot be due to the pathologic conditions present in the hearts of these patients, for they all show some form of arteriosclerosis of the coronary arteries. It is established that the ischemia resulting from such coronary insufficiency enhances the tendency to develop ectopic foci.[23,24] Anoxemia, as these observations prove, likewise facilitates the appearance of ectopic foci in the ventricles during all forms of A-V dissociation. It is possible that in patients subject to transient seizures of ventricular fibrillation, anoxemia may enhance myocardial irritability sufficiently so that these ectopic foci become effective when they fall during the "vulnerable phase" of an ectopic beat and thus initiate fibrillation.[25] In this respect anoxemia may be said to be one of the coefficients responsible for the development of ventricular fibrillation in man.

SUMMARY AND CONCLUSIONS

1. Anoxemia was induced by the rebreathing method in two patients who were subject to transient seizures of ventricular fibrillation and in two patients with periodic standstill of the ventricles during auriculoventricular dissociation.

2. In one patient who developed transient ventricular fibrillation during transient A-V dissociation, progressive oxygen want easily converted a normal sinus mechanism to one of A-V dissociation. In two patients, further rebreathing during established A-V dissociation resulted in an acceleration of the auricular rate and the development of short runs of ventricular fibrillation.

3. In two patients who were known to have syncopal attacks due to periodic standstill of the ventricles, rebreathing resulted in an acceleration of the auricles with the appearance of premature beats of the ventricles. Occasionally the A-V rate became more rapid and irregular.

4. The appearance of these arrhythmias following rebreathing was irregular and varied from four to nineteen minutes after the beginning of the experiment.

5. Anoxemia is one of the factors responsible for the development of transient seizures of ventricular fibrillation in patients who are subject to such seizures during A-V dissociation.

REFERENCES

1. Greene, C. W., and Gilbert, N. C.: Studies on the Responses of the Circulation to Low Oxygen Tension. The Causes of the Changes Observed During Extreme Anoxia, Am. J. Physiol. **60**:155, 1922.
2. Barcroft, J.: The Respiratory Function of the Blood, 1925, Cambridge University Press, p. 111.
3. Wiggers, C. J.: Cardiac Adaptation in Acute Progressive Anoxia, Ann. Int. Med. **14**:1237, 1941.
4. Lewis, T., and Mathison, G. C.: Auriculoventricular Heart Block as a Result of Asphyxia, Heart **5**:289, 1913.
5. Mathison, G. C.: The Cause of Heart Block Occurring During Asphyxia, Heart **5**:54, 1910.
6. Lewis, T., and Oppenheimer, B. S.: The Influence of Certain Factors Upon the Asphyxial Heart Block, Quart. J. Med. **4**:145, 1910.
7. Lewis, T., Meakins, J., and White, P. D.: The Susceptible Region in A-V Conduction, Heart **5**:289, 1913.
8. Resnick, W. H.: Observations on the Effects of Anoxemia on the Heart, J. Clin. Investigation **2**:93, 1925.
9. Criep, L. H.: Electrocardiographic Studies on the Effects of Anaphylaxis on the Cardiac Mechanism, Arch. Int. Med. **48**:1098, 1931.
10. Rothschild, M. A., and Kissin, M.: Induced General Anoxemia Causing S-T Deviation in the Electrocardiogram, Am. Heart J. **8**:745, 1932.
11. Rothschild, M. A., and Kissin, M.: Production of Anginal Syndrome by Induced General Anoxemia, Am. Heart J. **8**:729, 1933.
12. Katz, L. N., Hamburger, W. W., and Shutz, W. J.: The Effects of Generalized Anoxemia on the Electrocardiograms of Normal Subjects. Its Bearing on the Mechanism of Attacks of Angina Pectoris, Am. Heart J. **9**:771, 1933.
13. Levy, R. L., Barach, A. L., and Bruenn, H. G.: Effects of Induced Oxygen Want in Patients With Cardiac Pain, Am. Heart J. **15**:187, 1938.
14. May, S. H.: Electrocardiographic Response to Gradually Induced Oxygen Deficiency, Am. Heart J. **17**:655, 1939.
15. Greene, C. W., and Gilbert, N. C.: Studies in the Responses of the Circulation to Low Oxygen Tension. III. Changes in the Pacemaker and in Conduction During Oxygen Want as Shown in the Human Electrocardiogram, Arch. Int. Med. **27**:517, 1921.
16. Schwartz, S. P., and Jezer, A.: The Action of Adrenalin in Patients With Complete Heart Block and Stokes-Adams Seizures, Am. Heart J. **7**:652, 1932.

17. Schwartz, S. P., and Jezer, A.: The Effects of Intravenous Administration of Digitalis Bodies on Patients With Transient Ventricular Fibrillation, AM. HEART J. **16**:462, 1938.
18. Schwartz, S. P., and Jezer, A.: Studies in Transient Ventricular Fibrillation. III. The Prefibrillatory Mechanism During Established Auriculoventricular Dissociation, Am. J. M. Sc. **192**:153, 1936.
19. Means, J. H., and Newburgh, L. H.: Studies of the Blood Flow by the Method of Kroh and Lindhard, Tr. A. Am. Physicians **30**:51, 1915.
20. Lundsgaard, C.: Studies of Oxygen in the Venous Blood, J. Exper. Med. **27**:179, 1918.
21. Peters, J. P., Jr., and Barr, D. P.: Carbon Dioxide Curve and Carbon Dioxide Tension of Blood in Cardiac Disease, J. Biol. Chem. **45**:537, 1921.
22. Siebeck, R.: Ueber Kardiale Dyspnoea, Klin. Wchnschr. **8**:2121, 1929.
23. Wiggers, C. J., Wegria, R., and Pinera, B.: The Effects of Myocardial Ischemia on the Fibrillation Threshold. The Mechanism of Spontaneous Ventricular Fibrillation Following Coronary Occlusion, Am. J. Physiol. **131**:309, 1940.
24. Carter, E. P., and Andrus, E. C.: A Consideration of the Cardiac Arrhythmias on the Basis of Local Circulatory Changes, Arch. Int. Med. **34**:669, 1924.
25. Wiggers, C. J.: The Mechanism and Nature of Ventricular Fibrillation, AM. HEART J. **20**:399, 1940.

ON T WAVES NORMAL IN SIZE AND DIRECTION BUT ABNORMAL IN CONTOUR

V. Alzamora-Castro, M.D., Carlos Rubio, M.D., Guido Battilana, B.S., and Ricardo Subiría, B.S.

MANY different abnormalities of the QRS complexes have been described, and a large number of these are easily recognized and have been shown to have a more or less precise significance. On the other hand, the different abnormalities of the T complex that have come to be widely recognized as distinctive and as having a definite connotation are few. Abnormalities in the direction of the T wave have received a great deal of attention and several different varieties of inverted T waves are distinguished. Abnormalities of the size of upright T waves have also been described, although these are recognized with greater difficulty than abnormalities in the direction, and their meaning is less clearly understood. Comparatively little has been done toward the analysis of abnormalities of the shape of upright T waves, although it is known, for example, that potassium retention in some cases of uremia may give rise to a tall, pointed T wave of more or less distinctive outline.[1,2]

The purpose of this article is to call attention to certain types of upright T waves which differ in shape from normal T waves and become inverted under a variety of circumstances, alike in certain particulars.

MATERIAL AND METHODS

We have examined 100 normal electrocardiograms collected by Bryant.[3] The ages of the subjects studied by him ranged from 19 years to 32 years. He recorded the standard and unipolar limb leads and precordial Leads V_2 and V_4. We have taken in Lima and in Ann Arbor 100 additional electrocardiograms on normal subjects 20 to 75 years of age. This series includes seven precordial leads (V_1, V_2, V_3, V_4, V_5, V_6, and V_E), as well as the six limb leads. In 80 of these 100 cases the effect of carotid sinus massage was investigated. In forty instances, all of the thirteen leads mentioned were taken before, and at least Leads I, II, V_R, V_F, V_3, V_4, V_5, and V_6 were taken during this procedure. In the remaining forty cases it was studied in a smaller number of leads. The age of the subjects upon which this test was performed ranged from 20 to 75 years, with an average age of 37 years. The effect of carotid sinus massage upon the form of the T wave

From the Hospital "Dos de Mayo," Lima, Perú, the Medical School of University of San Marcos, and the Department of Internal Medicine of the University of Michigan Medical School.

Many of the observations upon which this article is based were made with the assistance of a fellowship from the W. K. Kellogg Foundation and with the aid of grants to Doctor Frank N. Wilson from the Horace H. Rackham School of Graduate Studies and the S. S. Kresge Foundation.

was also studied in a series of 600 patients with various types of heart disease. In this group, tracings were taken only when inspection of movements of the galvanometer string shadow indicated that changes were taking place. Blood pressure readings were taken during the period of carotid sinus stimulation in many instances. When this procedure produced changes in form of the T wave the patient was kept under observation and additional tests were made during a period which varied from a few months to one and one-half years. All electrocardiograms were taken with the patient in the recumbent position. The precordial points from which leads were taken were carefully marked. All records were taken with an electrocardiograph of the string galvanometer type.

OBSERVATIONS

The T Waves of Normal Subjects.—In describing the T waves of the normal records, we may ignore the variations in the polarity and contour of this deflection in Lead III and in Leads V_L and V_1, which are well known. We may also pass over variations of like kind in Leads V_F, V_2, and V_E. The form of the T wave in the remaining leads (I, II, V_R, V_3, V_4, V_5, and V_6) was much more constant.

In all these leads, except V_R, the normal T wave is upright and has a more or less characteristic shape. The slope of its ascending limb is much more gradual than that of its descending limb (Fig. 1,*A* to *E*). The normal T wave of Lead V_R would have the same shape if its direction were reversed (Fig. 1,*F*). The difference between the two limbs of the T wave is well brought out by dropping a perpendicular upon the base line from the apex of this deflection. The angle made with this perpendicular by the tangent of the first limb is much larger than that made by the tangent of the final limb (Fig. 1,*A* to *F*). These angles were measured in approximately forty cases. Their absolute and relative magnitudes vary greatly with the height and the shape of the apex of the T wave. For that reason we shall not present a detailed analysis of these measurements.

In the vast majority of instances both limbs of the T wave were smooth and the changes in their slopes from point to point were gradual. The final slope was often followed by a U wave of small size. In ten normal subjects, 5 per cent, the T waves in one or more leads did not correspond to this description. In some cases the two angles mentioned were approximately equal, the peak of the T wave was unusually sharp or unusually blunt, notching was present, or some other peculiarity in form occurred. Unusual oscillations at the very end of the T wave, possible U waves, sometimes were observed. Because T waves showing these features occurred in only a small percentage of cases, we consider them atypical (Fig. 1,*G* to *X*).

Atypical T Waves in the Electrocardiograms of Patients With Various Diseases.—In the tracings of patients with heart disease, atypical T waves were much more frequent than in the records of normal subjects, and the atypical features were much more pronounced. In many electrocardiograms of such patients the atypical T waves were frequently the only peculiarity suggesting that the heart was abnormal. We have, however, no reliable statistical data upon which an

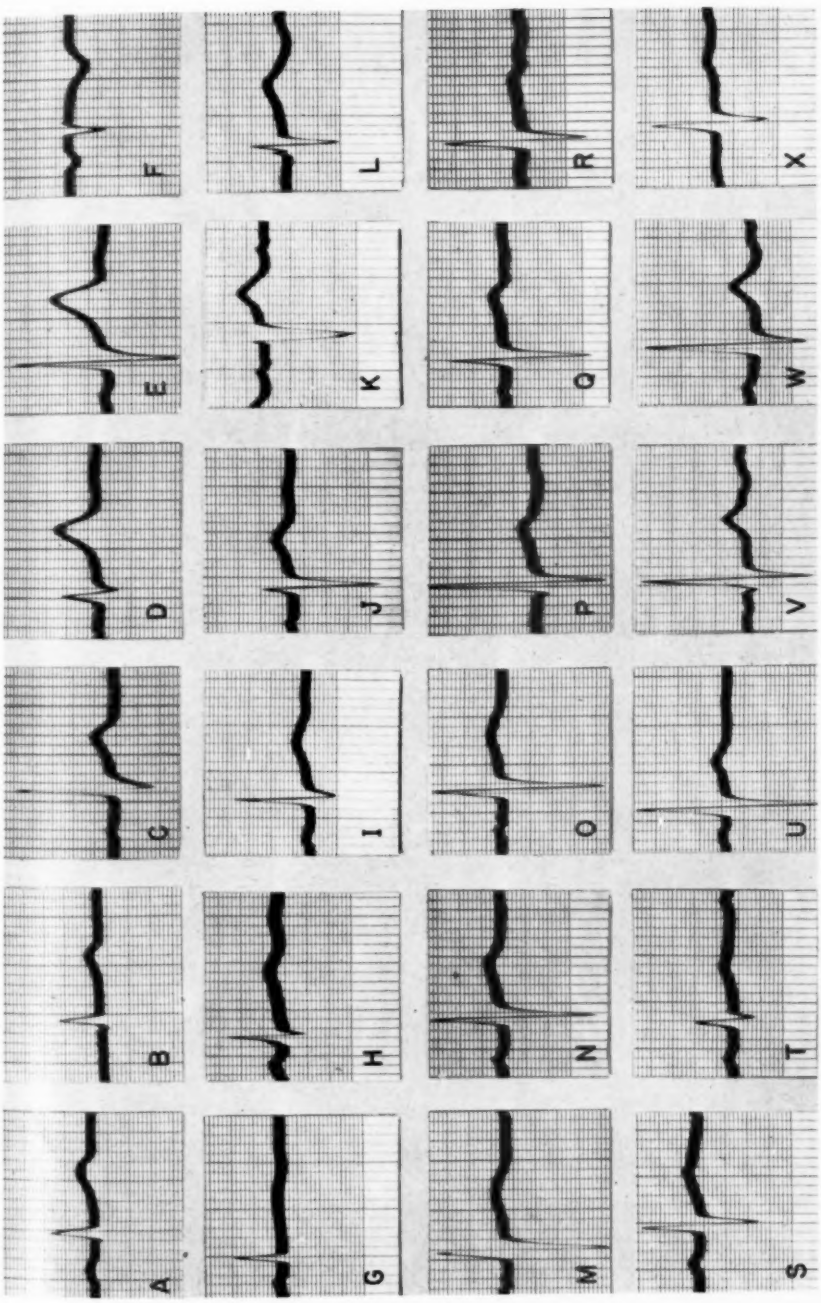


Fig. 1.—The T waves of the complexes shown in Strips *A* to *F*, inclusive, are regarded as normal in shape. The inverted T wave of Strip *F* illustrates the normal appearance of this deflection in Lead V_R. The T waves of the remaining strips, *G* to *X*, inclusive, are regarded as atypical in shape. In some instances the two angles made by the tangents of the ascending and the descending limbs of the T deflection with a perpendicular to the isoelectric level drawn through the summit of this deflection are approximately equal (*G*, *H*, *I*, *J*, *M*, *S*, *T*, *U*, *V*, and *W*), or the angle made with this perpendicular by the tangent to the descending limb is larger than that made by the tangent to the ascending limb (*K* and *L*). In other instances the apex of the T wave is usually sharp (*V*) or unusually blunt (*G* and *M*). In still other cases there is an irregularity or notch on the descending limb of the T deflection (*O*). In such cases carotid sinus pressure may cause inversion beginning in the vicinity of the notch or irregularity. Sometimes there are oscillations at the very end of the T wave (*P*, *Q* and *R*) which differ in character from the normal U wave. Carotid sinus stimulation often produces inversion beginning near the very end of the T wave under these circumstances.

accurate estimate of the frequency of atypical T waves in tracings of patients with heart disease can be based. They were encountered under a variety of conditions. They occurred in precordial leads taken from points near those which yielded inverted T waves, and were found in tracings taken during attacks of angina pectoris[4] and in tracings taken after exercise tests.[5] Similar deflections were found in the tracings of patients who were convalescing from acute illness or who were suffering from a severe metabolic disorder, frequently when the heart was known to be involved. Atypical T waves often seemed to be associated with a prolongation of the Q-T interval, but in many such instances the end of the T waves could not be determined with sufficient accuracy to make it possible to measure this interval satisfactorily.

Carotid Sinus Stimulation.—In normal subjects carotid sinus stimulation produced slight variations in the amplitudes and contour of the T wave. In no instance did it alter the polarity of this deflection. The maximal change in amplitude was 1.1 mm. and the average change was 0.2 millimeter. In 52 per cent of the cases no modifications of the T wave were observed. Naturally, bradycardia occurred in practically all instances.

In the electrocardiograms of patients with cardiac abnormalities inverted T waves often became more inverted during carotid sinus massage. In only two cases did such T waves become upright. In Lead V_R, in which the T wave is normally inverted, any change which occurred was opposite in character to those which took place in the leads from the left side of the precordium. Atypical upright T waves of the kind described in the preceding paragraph often became inverted during carotid sinus stimulation. Sometimes the inversion was confined to the terminal part of the deflection and was of the V-shaped type. We may leave out of consideration here such changes in the T waves as accompanied the development of an independent ventricular rhythm. This phenomenon seldom occurred.

Carotid sinus massage induced, of course, both bradycardia and a fall in the blood pressure. It is impossible to say whether the T-wave changes observed were due directly to the change in the heart rate, to the change in the blood pressure, or to these combined with other factors.[6,7] In many cases of chronic heart disease in which T-wave changes were observed following carotid sinus stimulation, serial electrocardiograms were taken over a period of several months. In some of the instances in which carotid sinus stimulation produced temporary inversion of previously upright T waves, persistent inversion of these deflections was observed days or weeks later. In other cases, T waves which were persistently inverted when the patient was first seen became upright later, and in many such instances temporary inversion could then be induced by carotid sinus stimulation. We may, therefore, say that carotid sinus stimulation frequently produces temporary changes in the T waves of the kind that will become persistent subsequently, or temporary T-wave changes of a kind that were persistent in the past.[6]

The leads in which the T waves became inverted on carotid sinus stimulation were rather constant for the same individual, but varied from one patient to another. This suggests that the phenomenon under consideration is determined

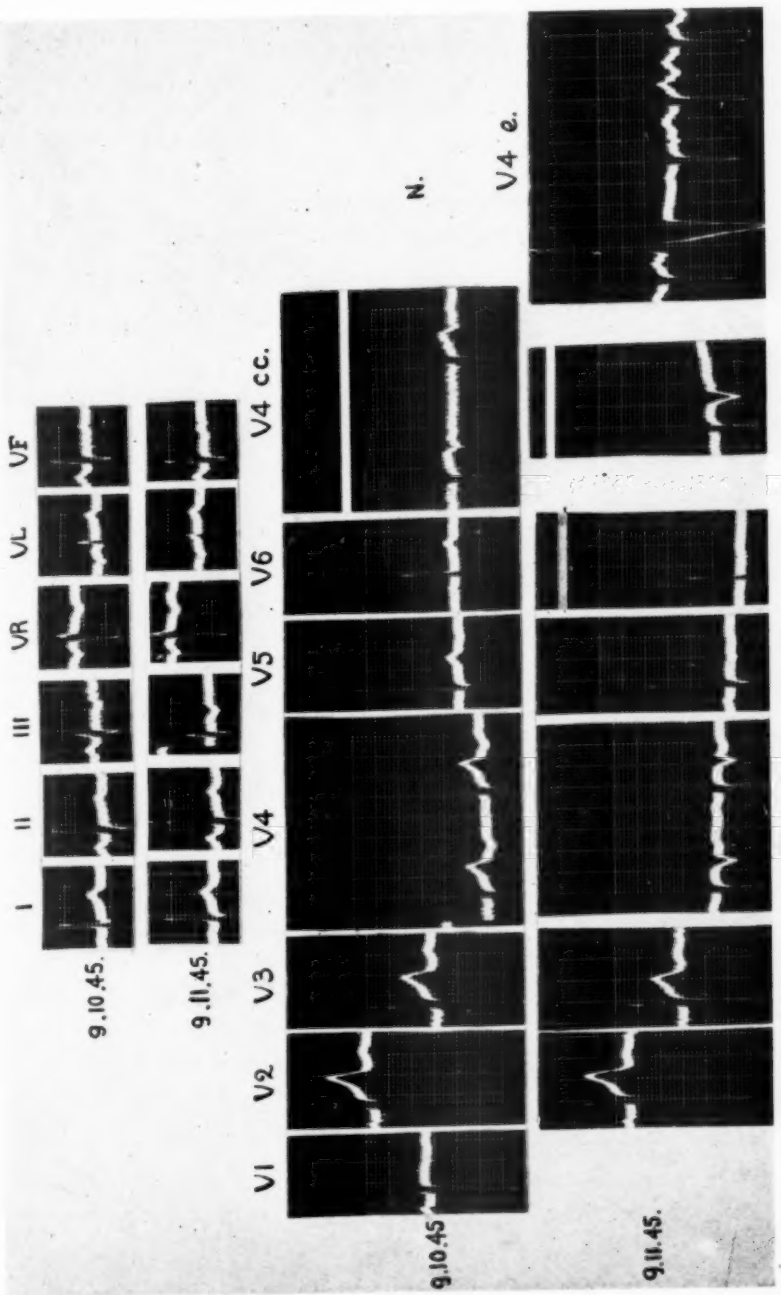


Fig. 2.—Electrocardiograms in Case 1. See text for explanation.

by the underlying condition of the heart, and even by conditions existing locally in the myocardium. In some cases in which the T waves were extremely labile, it was possible to change the polarity of this deflection at pleasure.[7]

During carotid sinus massage the T waves of some hypertensive individuals became inverted when the heart rate was relatively fast and the blood pressure was still above the normal range. In such cases the T-wave changes cannot be ascribed to abnormal variations in the heart rate or in the blood pressure. That carotid sinus stimulation can exert direct effects upon the ventricular myocardium seems improbable because all attempts hitherto have failed to demonstrate any direct action of the vagus nerves on the ventricular muscle. Sometimes the inversion of the T waves induced by massage of the carotid sinus region persisted for a considerable period and only became upright when the heart rate and the blood pressure had returned approximately to their original levels.

Frequently the inversion of the T waves produced by carotid sinus stimulation was the sole electrocardiographic abnormality detectable, but the suspicion that the heart was abnormal which it aroused was supported by the clinical data. The most striking changes in the T waves were recorded in patients with arteriosclerotic and hypertensive heart disease, but the same phenomena were occasionally observed in syphilitic, rheumatic, and congenital heart disease.[6,7]

ILLUSTRATIVE CASES

CASE 1.—The patient was a man, aged 55 years, whose blood pressure had been elevated for several years. The electrocardiograms taken on Sept. 10, 1945, were not definitely abnormal, but the contour of the T waves as atypical, particularly in Lead V_4 (Fig. 2). On carotid sinus stimulation, these atypical T waves became inverted ($V_4\,c\,c$). On the following day the patient's clinical condition and the deflections of the limb leads were unchanged, but the T wave was inverted in Lead V_4 and flat in Leads V_5 and V_6. Carotid sinus stimulation increased the depth of the inverted T wave in Lead V_4 (V_4, $c\,c$), but produced no changes in the other leads. After exercise the patient complained of retrosternal oppression and the T waves in Lead V_4 became upright (V_4, e); at this time, however, the T waves of the complexes which followed compensatory pauses due to extrasystoles were flat or showed slight terminal inversion. All of the T waves were inverted when the effect of the exercise had worn off. Serial electrocardiograms taken at intervals over a period of one year showed striking changes in the shape of the T waves not associated with changes in the patient's clinical status.

CASE 2.—The electrocardiograms reproduced in Fig. 3 are those of a man, aged 53 years, who had hypertensive heart disease. In the records taken on Sept. 25, 1947, the T waves are flat in Lead II and slightly inverted in Lead V_F. The Q-T interval is somewhat prolonged and, following long postextrasystolic diastoles, there is flattening of this deflection in Lead I. In the tracings of the following day the T waves of precordial Leads V_5 and V_6 were somewhat atypical before and definitely inverted during carotid sinus stimulation ($V_5\,c\,c$ and $V_6\,c\,c$); stimulation also induced moderate changes in the T deflection in Lead V_4 ($V_4\,c\,c$).

CASE 3.—The electrocardiograms reproduced in Fig. 4 are those of a man, aged 51 years, with hypertensive heart disease. The tracing of May 5, 1946, shows left axis deviation and flat T waves in Lead II. On Jan. 14, 1947, one month after splanchnicectomy, the T waves were taller and the heart rate was faster. On Oct. 25, 1947, electrocardiograms were taken before and after carotid sinus stimulation. The classical limb leads labelled *a* were taken before and the tracings *b* during carotid sinus stimulation. The precordial leads were apparently normal, but the T waves in Leads V_4 and V_5 were atypical, and of the type that very often become inverted during carotid sinus stimulation. During carotid sinus massage the heart rate decreased,

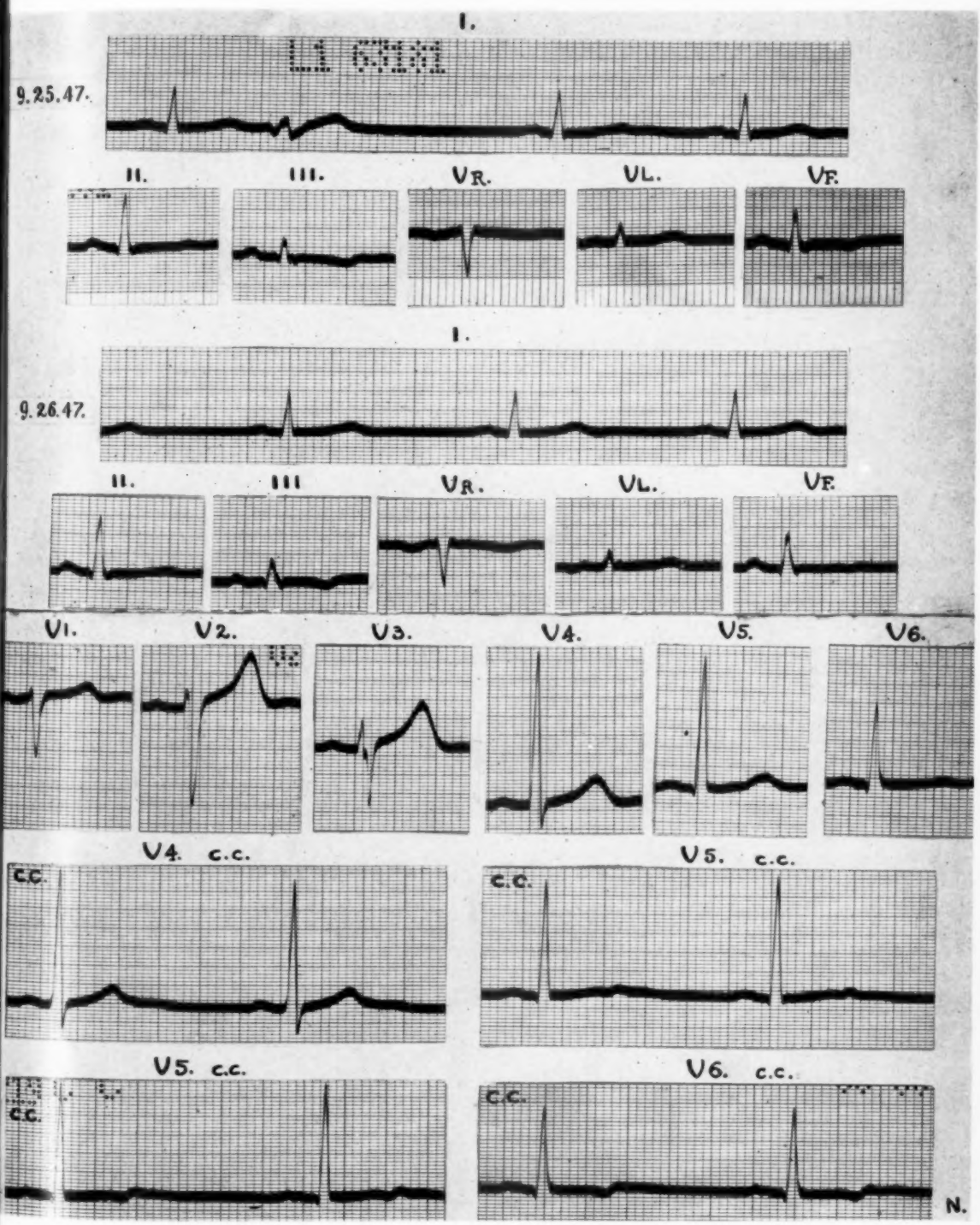


Fig. 3.—Electrocardiograms in Case 2. See text for explanation.

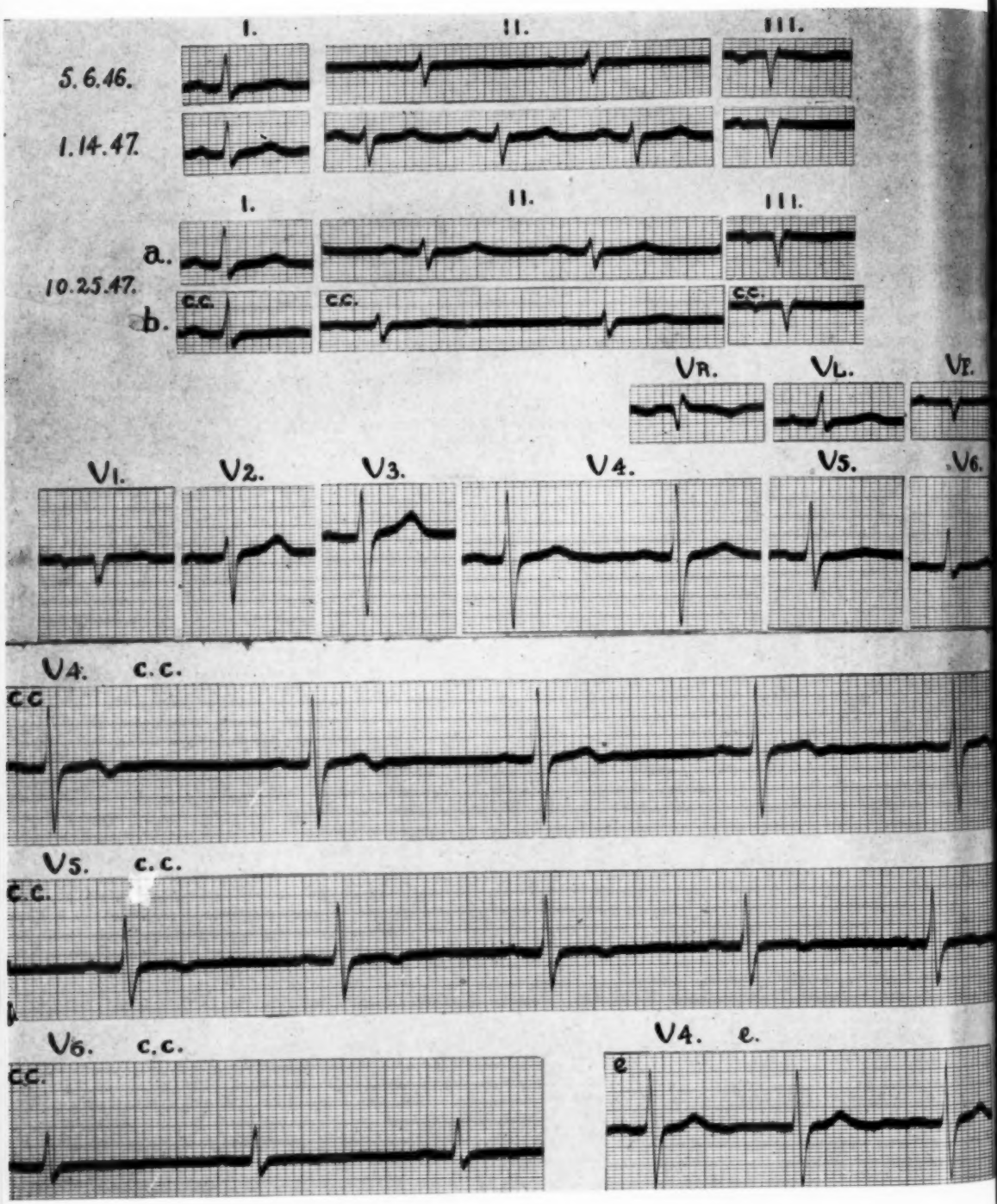


Fig. 4.—Electrocardiograms in Case 3. See text for explanation.

the blood pressure fell from 160/110 to 122/88, and the T waves became inverted in these leads ($V_4\,c\,c$ and $V_5\,c\,c$). In Lead V_6 the T deflections became nearly isoelectric ($V_6\,c\,c$). The tracing marked $V_4\,e$ was recorded after moderate exercise. Here the T waves are upright but atypical. In the electrocardiograms taken a few hours later the T waves were flat in Leads II, V_4, V_5, V_6, and V_R.

CASE 4.—The patient was a man, aged 62 years, who was having severe attacks of angina pectoris. The electrocardiograms showed inversion of the T waves which became more pronounced during carotid sinus stimulation. The complexes reproduced in Fig. 5 were selected from a continuous tracing taken during an attack of angina pectoris. During the attack the T waves became upright and there was slight downward displacement of the RS-T junction. The Q-T interval was considerably prolonged while the T wave was upright, and this deflection was definitely atypical in form. Note that it is distinctly notched and that the final limb falls very slowly. In other electrocardiograms taken on the same patient during attacks of angina pectoris, reversal of polarity of the T waves was observed with simultaneous pronounced RS-T displacement. In Lead V_R the displacement was upward and was accompanied by terminal inversion of the T wave; in Leads V_3, V_4, V_5, and V_6 the displacement was downward and the terminal part of the T wave was upright.

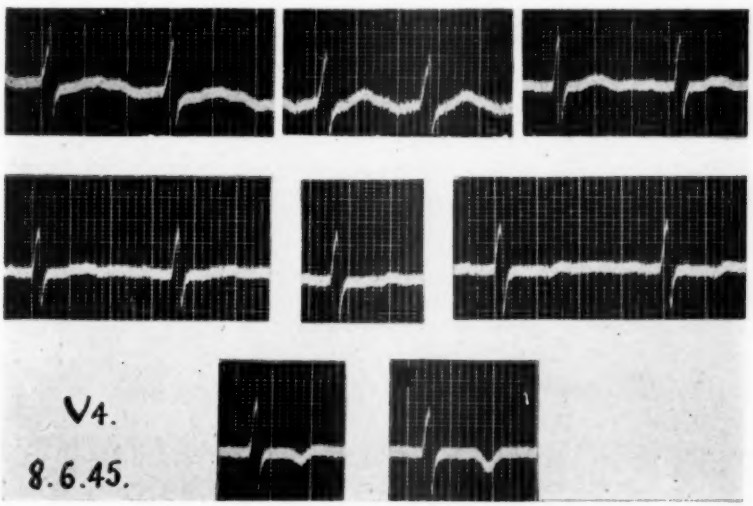


Fig. 5.—Electrocardiograms in Case 4. The complexes reproduced were selected from a continuous tracing taken during an attack of angina pectoris. During the attack the T waves became upright and these deflections were definitely atypical in form. The Q-T interval was considerably prolonged while the T deflection was upright.

CASE 5.—A 56-year-old man complained of pain in the left upper quadrant of the abdomen. The blood pressure was 190/130 and there was a history of mild angina pectoris. Electrocardiograms taken on Aug. 20 and Sept. 1, 1946, were similar to those taken on Sept. 3, 1946, which are reproduced in Fig. 6, *a*. The T waves are flat in all the limb leads and inverted in precordial Leads V_3, V_4, V_5, and V_6. Prolonged carotid sinus massage produced moderate bradycardia, and a fall in the blood pressure to 120/80 for a period of at least one-half hour. During this time the T waves became progressively more inverted in the precordial leads, the previously isoelectric deflections in Leads I, II, and III became inverted, and those of Lead V_R became upright (Fig. 6, *b*). Moderate exertion produced tachycardia, with a rise in the blood pressure to 240/140. The T waves became upright. Tracing V_3, *e* shows a series of complexes from a continuous tracing. The first strip is the control and the other strips show the progression of the changes following the exercise test. On Sept. 18, 1946, the patient felt stabbing pain in

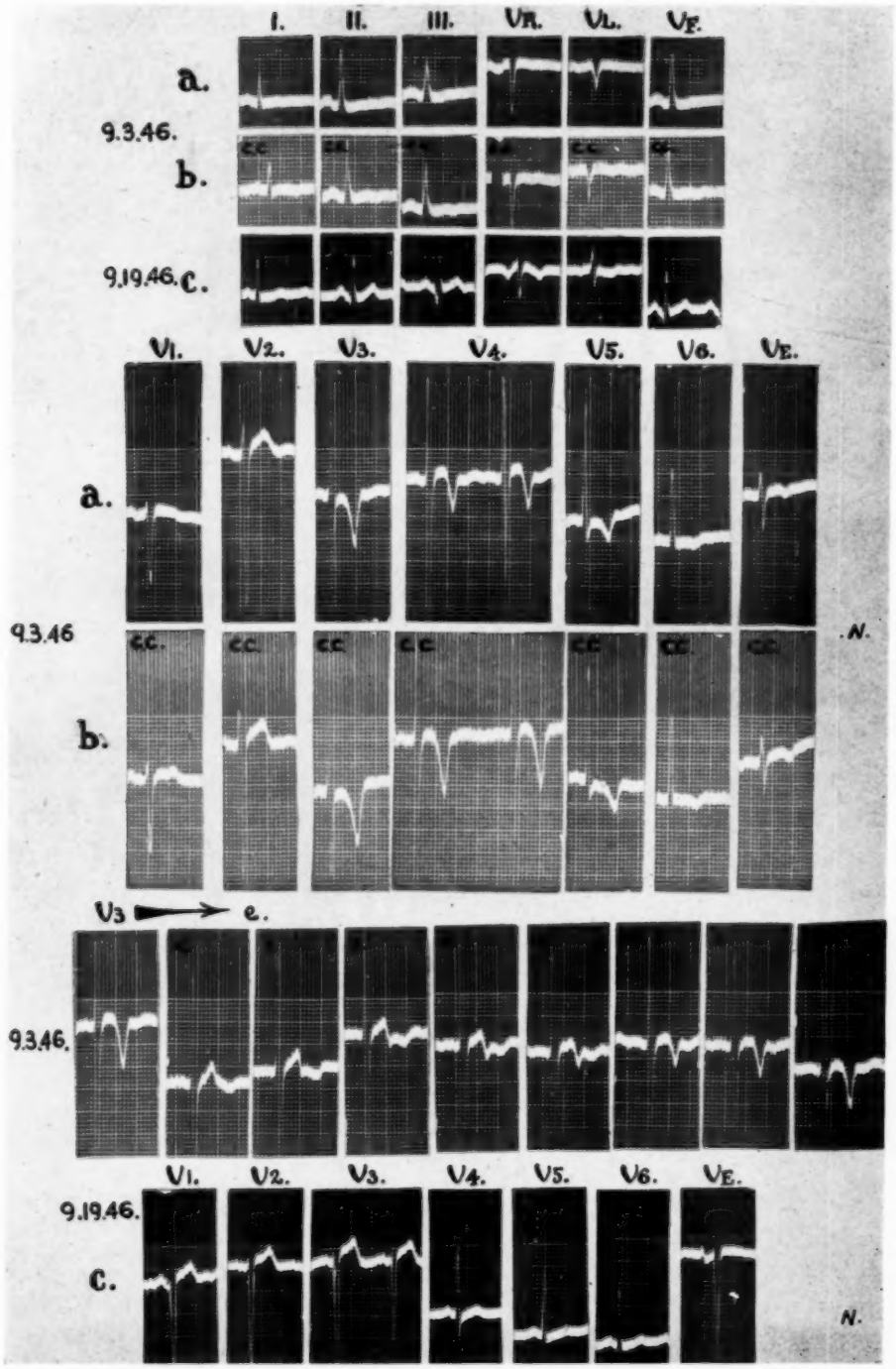


Fig. 6.—Electrocardiograms in Case 5. The electrocardiograms labelled *a* were taken before, and the tracings *b* during prolonged carotid sinus massage. Tracing V_3, *e* shows the progression of the changes following an exercise test. The electrocardiograms labelled *c* were taken several hours after an episode suggesting myocardial infarction.

the left upper quadrant with radiation to the left arm and precordium. On the following day his condition was precarious; shock was severe and the blood pressure fell to 120/75. The electrocardiograms taken at this time showed a pronounced reduction in the size of the R waves in Leads V_2 and V_3, slight upward displacement of the RS-T segment in Lead V_3, and deep Q waves in Leads II, III, and V_F. The most striking change, however, was the reversal of polarity of the T waves in all leads (Fig. 6, *c*). This pnenomenon was observed in a series of electrocardiograms taken during a one-half hour period. A fresh anteroseptal myocardial infarction was suspected. The patient died eighteen hours later. The autopsy showed general arteriosclerosis and fresh myocardial infarction. The lower part of the septum and a small area in the anterior ventricular wall were affected. The subendocardial layers and papillary muscles were predominantly involved. The necrotic process was found to be more advanced in some places than in others. The coronary arteries, chiefly the anterior descending branch of the left coronary, were partially occluded. There was, however, no complete coronary occlusion. Nearly two liters of blood were found in the left pleural cavity, the hemothorax being due to the rupture of an aneurysm of the descending aorta.

DISCUSSION

In the electrocardiograms of normal persons the contour of the T waves varies within rather narrow limits. In the tracings of patients with obvious or suspected heart disease, however, T waves of atypical shape are fairly common. Many of these atypical T deflections become inverted during carotid sinus pressure, after long postextrasystolic diastoles, or in the course of time even when there has been no definite change in the patient's clinical status. On the other hand, inverted T waves, particularly those in which the inversion is sharp and terminal, are often converted into atypical upright T waves by exertion, or other circumstances which increase the load upon the heart. The same reversal in polarity may occur during an attack of angina pectoris or even in the course of myocardial infarction. The changes in the T waves under consideration may be accompanied by changes in the level of the RS-T junction. They are not secondary to changes in the form of the QRS complex. Consequently, these T-wave changes are of the kind called primary by Wilson and Finch[8]; they depend upon changes in the ventricular gradient,[9,10] or, in other words, upon variations in the repolarization process, presumably dependent upon factors which affect the ventricular myocardium locally.

In 1931, Wilson, Macleod, and Barker[9] pointed out that in normal subjects the ventricular gradient points from the base toward the apex of the heart and suggested that this means that the average length of systole is greater in the base of the heart than at the apex, or greater on the inner than on the outer aspects of the ventricular walls, or both.

Recently a number of investigators have published electrocardiograms obtained by introducing an exploratory electrode into the cavity of the human right ventricle.[11,12,13] When the heart is normal the T waves inscribed in such leads are sharply and deeply inverted. In leads from the right side of the precordium, the QRS deflections are similar in general outline to those of the internal leads, but the T waves are strongly positive. It is evident, therefore, that although the subendocardial muscle of the right ventricle passes into the active state in advance of the subepicardial muscle, it passes out of this state later. In other words, the duration of the excited state is longer on the inner than on the outer aspect of

this wall. Whether or not this is also true of the left ventricular wall is uncertain. The T wave is normally sharply inverted in Lead V_R, which presumably reflects the potential variations of both of the ventricular cavities, and this strongly suggests that the cavity of the left ventricle, like that of the right, is negative during the inscription of this wave. It is true that Wilson and Herrmann,[14] in experiments in dogs, found that the deeper layers of the left ventricular wall pass out of the refractory period earlier than the superficial layers. In their experiments, however, the heart was exposed, and cooling and drying of the epicardial surface may have increased the duration of the excited state of the outermost layers of the muscle. There are, furthermore, no data bearing upon the form of the T deflection in direct epicardial leads or in leads from the ventricular cavities in these experiments. Byer, Ashman, and Toth[15] in experiments in dogs in which the chest was not opened have shown that cooling the endocardial surface of the heart prolongs the Q-T interval and greatly increases the size of the normally upright T waves in leads from the precordium.

We may conclude, tentatively, that the duration of the excited state is greater on the inner than on the outer surface of the ventricles, and, consequently, that the cavities of both ventricles are negative and the epicardial surfaces of both ventricles are positive during the inscription of the T deflection. If this is the case, reversal in polarity of the T wave is the result of a change in the relative length of systole on the two surfaces of the ventricular walls. No detailed explanation of this phenomenon is possible until we know what factors determine the normally greater duration of systole on the inner aspect of the ventricular walls, and how they are modified by various procedures. Some of the factors that come to mind are: blood supply, temperature, the influence of the vegetative nervous system, differences in tension in the various parts of the ventricular walls during ventricular contraction, and inherent differences in the muscle of different parts of the myocardium. There are at the present time few data bearing upon the influence or lack of influence of these factors or of others that may be involved. It has, however, been shown that local ischemia of the ventricular wall, produced by compression of a coronary artery, induces sharp inversion of the T waves in direct leads from the epicardial surface.[15] It has not been shown that the T waves of unipolar cavity leads are affected in the opposite manner, although it seems probable that this is the case. A more severe grade of ischemia leads to elevation of the RS-T segment in the epicardial leads and presumably to downward RS-T displacement in the cavity leads.

In a case of syphilitic aortitis reported elsewhere, the coronary blood flow was evidently greatly decreased. During life the patient had very frequent attacks of anginal pain. The autopsy showed that the coronary ostia were almost completely obliterated although the coronary arteries themselves were not involved. There was extensive necrosis of the subendocardial muscle of the left ventricle including that of the septum and the papillary muscles. In the right ventricular wall, patchy necrosis was present.[17] The subendocardial arteriolar plexus, described by Gross,[18] and the Thebesian vessels did not prevent necrosis, and only the Purkinje network remained undamaged.[17] These findings suggest that when the coronary circulation is uniformly impaired, lesions are likely to

occur in those places where systole is thought to be longest in normal subjects. It is probable that the physiologic, mechanical, and circulatory conditions are not entirely uniform throughout the left ventricular walls.[17,19,20] During the attacks of angina pectoris in this case, the electrocardiographic abnormalities consisted of downward displacement of the RS-T segment in the leads from the left side of the precordium and upward RS-T displacement in Lead V_R. Similar electrocardiographic changes have often been recorded during attacks of angina pectoris,[21-25] and there is some evidence that when anginal seizures are severe and persistent, necrosis of the subendocardial layers of the left ventricle is not infrequent. In 1932 Buchner[26] demonstrated that in the hearts of patients with angina pectoris necrosis was confined chiefly to the inner layers and papillary muscles of the left ventricle. Other studies have confirmed these observations, and RS-T displacement of the type described has been related to subendocardial injuries.[17,19,25,27-30]

The reversal of polarity of inverted T waves in the precordial leads during attacks of angina pectoris and the downward displacement of the RS-T segment accompanying it strongly suggest ischemia of the subendocardial muscle of the left ventricle.[19] In one case in which this phenomenon was present, necrosis affecting chiefly the subendocardial and papillary muscles of the left ventricle was observed.[19] Sodi-Pallares, Vizcaíno, Soberón, and Cabrera[12] have reported a case in which the inversion of the T wave in a lead from the right ventricular cavity became more pronounced during a spontaneous attack of angina pectoris. They ascribed this phenomenon to subendocardial ischemia.

We have shown that exertion and carotid sinus stimulation may reverse the polarity of the T waves under certain circumstances. Both have pronounced effects upon the heart, mediated at least to a large extent, through the vegetative nervous system. It is, therefore, difficult to say whether the changes in the T waves which they induce depend directly upon the changes in the heart rate and its effects upon coronary blood flow, upon the mechanics of cardiac contraction, tension in ventricular walls, and so forth, or whether these effects are primarily due to alterations in sympathetic and vagal tone. Segers[31] has shown that mechanical factors such as the tension in the cardiac walls, and chemical factors such as the concentration of adrenalin, acetylcholine, potassium, and calcium have important effects upon the monophasic electrogram of the frog's heart and particularly upon the cardiac afterpotentials.[31] We have no data which justify any conclusion as to the exact mechanism by which exertion or carotid sinus stimulation produce the electrocardiographic effects described.

SUMMARY

In normal subjects the polarity and contour of the T waves are relatively constant. Atypical T waves of normal polarity occur only occasionally in the tracings of normal subjects, but are common in the electrocardiograms of patients with heart disease.

In many instances the behavior of these atypical T waves and the previous or subsequent clinical status of the patient indicate that the myocardium is abnormal.

During carotid sinus stimulation and after long postextrasystolic diastoles, many of these atypical upright T waves become inverted. On the other hand, many inverted T waves are converted into atypical upright T waves by exertion or angina pectoris.

In some cases atypical upright T waves furnish the only objective evidence that the heart is not normal.

We are deeply indebted to Dr. Frank N. Wilson for his helpful suggestions. We also desire to express our thanks to Dr. F. D. Johnston and Dr. J. M. Bryant for their kind interest in the preparation of this paper.

REFERENCES

1. Wilson, F. N., and Herrmann, G. R.: Some Unusual Disturbances of the Mechanism of the Heart Beat, Arch. Int. Med. **31**:923, 1923.
2. Keith, N. M., Burchell, H. B., and Baggenstoss, A. H.: Electrocardiographic Changes in Uremia Associated With High Concentration of Serum Potassium: Report of Three Cases, AM. HEART J. **27**:817, 1944.
3. Bryant, J. M.: The Distribution of Myocardial Action Currents in Relation to the Cardiac Silhouette, Master of Science Thesis, University of Virginia, 1946.
4. Alzamora-Castro, V.: Contribución al Conocimiento del Significado de las Modificaciones del Segmento S-T y de las Ondas T, Gac. méd. Lima **2**:285, 1946.
5. Alzamora-Castro, V.: I. Significado de Algunas Alteraciones de las Ondas T, Arch. Inst. Cardiol. México **16**:541, 1946.
6. Alzamora-Castro, V., and Rubio, C.: II. Significado de Algunas Alteraciones de las Ondas T, Arch. Inst. Cardiol. México **17**:98, 1947.
7. Alzamora-Castro, V., Rubio, C., Battilana, G., and Subiría, R.: I. Estudio y Significado de Algunas Ondas T Anormales. Los Efectos de la Compresión Seno-Carotídea, Rev. argent. de cardiol. **14**:163, 1947.
8. Wilson, F. N., and Finch, R.: The Effect of Drinking Iced-Water Upon the Form of the T-Deflection of the Electrocardiogram, Heart **10**:275, 1923.
9. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The T-Deflection of the Electrocardiogram, Tr. A. Am. Physicians **46**:29, 1931
10. Wilson, F. N., Macleod, A. G., Barker, P. S., and Johnston, F. D.: The Determination and the Significance of the Areas of the Ventricular Deflections of the Electrocardiogram, AM. HEART J. **10**:46, 1934.
11. Hecht, H. H.: Potential Variations of the Right Auricular and Ventricular Cavities in Man, AM. HEART J. **32**:39, 1946.
12. Sodi-Pallares, D., Vizcaíno, M., Soberón, J., and Cabrera, E.: Estudio Comparativo del Potencial Intracavitario en el Hombre y en el Perro, Arch. Inst. Cardiol. México **17**:630, 1947.
13. Battro, A., and Bidoggia, H.: Endocardiac Electrocardiogram Obtained by Heart Catheterization in the Man, AM. HEART J. **33**:604, 1947.
14. Wilson, F. N., and Herrmann, G. R.: An Experimental Study of Incomplete Bundle Branch Block, and of the Refractory Period of the Heart of a Dog, Heart **8**:229, 1921.
15. Byer, E., Ashman, R., and Toth, L. A.: Electrocardiograms With Large Upright T Waves and Long Q-T Intervals, AM. HEART J. **33**:796, 1947.
16. Bayley, R. H., La Due, J. S., and York, D. J.: Further Observations on the Ischemia-Injury Pattern Produced In the Dog by Temporary Occlusion of a Coronary Artery. Incomplete T Diversion Patterns, Theophylline T Reversion, and Theophylline Conversion of the Negative T Pattern, AM. HEART J. **27**:657, 1944.
17. Alzamora-Castro, V.: IV. Contribución al Conocimiento del Significado de las Modificaciones del Segmento S-T. Angina de Pecho e Infartos Subendocardicos, Arch. Inst. Cardiol. México **17**:870, 1947.
18. Gross, L.: The Blood Supply of the Heart, New York, 1921, Paul B. Hoeber, Inc.
19. Alzamora-Castro, V., Rubio, C., Battilana, G., and Subiría, R.: II. Estudio y Significado de Algunas Ondas T Anormales. Su Vinculación con la Isquemia Subendocardica, Rev. argent. de cardiol. **14**:178, 1947.
20. Johnson, J. R., and Di Palma, J. R.: Intramyocardial Pressure and Its Relation to Aortic Blood Pressure, Am. J. Physiol. **125**:234, 1939.
21. Parkinson, J., and Bedford, D. E.: Electrocardiographic Changes During Attacks of Angina Pectoris, Their Bearing on the Origin of Anginal Pain, Lancet **1**:15, 1931.
22. Feil, H., and Siegel, M. L.: Electrocardiographic Changes During Attacks of Angina Pectoris, Am. J. M. Sc. **175**:255, 1928.

23. Wilson, F. N., and Johnston, F. D.: The Occurrence in Angina Pectoris of Electrocardiographic Changes Similar in Magnitude and in Kind to Those Produced by Myocardial Infarction, Tr. A. Am. Physicians **54**:210, 1939.
24. Wood, F. C., Wolferth, C. C., and Livezey, M.: Angina Pectoris. The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison With the Effects of Experimental Temporary Coronary Occlusion, Arch. Int. Med. **47**:339, 1931.
25. Bryant, J. M., and Wood, J. E.: Tobacco Angina, Am. Heart J. **34**:20, 1947.
26. Buchner, F.: Die Rolle des Herzmuskels bei der Angina Pectoris, Beitr. z. path. Anat. u. z. allg. Path. **89**:644, 1932.
27. Boyd, L. J., and Scherf, D.: The Electrocardiogram After Mechanical Injury of the Inner Surface of the Heart, Bull. New York M. Coll. **3**:1, 1940.
28. Master, A. M., Gubner, R., Dack, S., and Jaffe, H. L.: Differentiation of Acute Coronary Insufficiency With Myocardial Infarction From Coronary Occlusion, Arch. Int. Med. **67**:647, 1941.
29. Bayley, R. H.: The Electrocardiographic Effects of Injury at the Endocardial Surface of the Left Ventricle, Am. Heart J. **31**:677, 1946.
30. Wolferth, C. C., Bellet, S., Livezey, M. M., and Murphy, F. D.: Negative Displacement of the RS-T Segment in the Electrocardiogram and Its Relationships to Positive Displacement; An Experimental Study, Am. Heart J. **29**:220, 1945.
31. Segers, M.: Le Rôle des Potentiels Tardifs du Coeur, Mem. Acad. roy. de méd. de Belgique **1**:7, 1941.

CATHETERIZATION OF THE CORONARY SINUS IN MAN

JAMES W. CULBERTSON, M.D., MEYER H. HALPERIN, M.D., AND
ROBERT W. WILKINS, M.D.*
BOSTON, MASS.

THE technique of intravenous catheterization in man[1] is invaluable for clinical and physiological studies because it enables one to measure the pressure and sample the blood in the major vessels leading from the brain, liver, kidney, or right side of the heart. Cardiac and pulmonary arterial catheterization is performed most frequently in order to diagnose congenital defects of the heart or to determine cardiac output by the direct Fick method. In the course of such studies in this laboratory the catheter tip was placed inadvertently in the coronary sinus, without ill effect, in four of a series of twenty-five consecutive patients. The purpose of this communication is to report these cases and the data obtained concerning the pressure relationships and the oxyhemoglobin saturation of the blood in the human coronary sinus.

METHODS

Intravenous catheterization was performed with a Number 9 USCI cardiac and large vein catheter,† which was inserted into a tributary of the right basilic vein and passed via the basilic, axillary, subclavian, and innominate veins and the superior vena cava into the right atrium, and from there presumably into the right ventricle. An indwelling 18 gauge needle was inserted through procainized skin into the femoral artery. Pressures were taken with Hamilton manometers,[2] while high frequency ballistocardiograms[3] and pneumograms were recorded by suitable tambours in the same optical system. After preliminary clearing of the catheter and needle of saline or sodium citrate solution by the withdrawal of ample amounts of blood, venous and arterial samples were taken in oiled syringes containing sufficient heparin solution (1 per cent) to fill the dead space in the tip. The samples were handled anaerobically and stored over mercury in a refrigerator. They were analyzed in duplicate within eight hours for content of oxygen by the technique of Van Slyke and Neill.[4] The allowable difference in duplicate analyses was 0.10 volume per cent. Hematocrit deter-

Presented before a meeting of the New England Heart Association, Boston, Mass., March 31, 1947 (Proc. New England Heart Assoc., 1945-1947, pp. 58-59).

*From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston, Mass.

†These catheters are manufactured in various sizes (French scale) by the United States Catheter and Instrument Corporation, Glens Falls, N. Y. Since these observations were made, No. 10 catheters have proved to be more generally satisfactory for routine cardiac, hepatic, and renal catheterization procedures in this laboratory.

minations also were made in duplicate on each sample in order to exclude errors caused by possible slight dilution of the sample withdrawn through the catheter. Any necessary small corrections were included in calculation of the venous oxyhemoglobin saturation and the arteriovenous oxygen difference.

CASE REPORTS

CASE 1.—A 52-year-old woman entered the hospital with a scabious dermatitis and mild diabetes mellitus which was controlled by dietary means alone. The cardiovascular system was essentially normal. In the course of an attempt to measure the cardiac output by the direct Fick method (Nov. 8, 1946) the catheter tip was placed in a position thought to be near the conus arteriosus of the right ventricle. However, when subsequent analysis of the three samples of blood withdrawn through the catheter revealed their oxyhemoglobin saturation to be surprisingly low and the calculated cardiac output to be absurdly small, it was suspected that the catheter tip had been elsewhere (Table I). Moreover, the photographic record of pressure changes transmitted through the catheter manifested an unfamiliar pattern (Fig. 1).

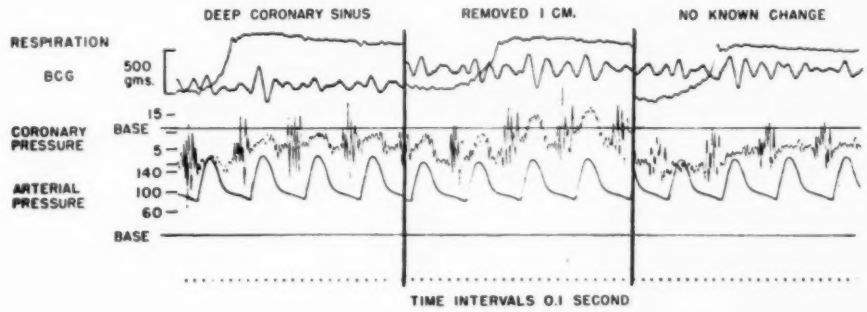


Fig. 1.—Optical records of respiration (expiration upward), ballistocardiogram, coronary venous pressure, and femoral arterial pressure in Case 1. The pressure scales are in mm. Hg (Hamilton manometers). The first record was taken with the catheter tip probably in a venous tributary of the coronary sinus. Before the second record the catheter had been withdrawn slightly. Before the third it had not been manipulated.

Case 2.—A 25-year-old woman entered the hospital for diagnostic studies of a suspected patent ductus arteriosus. Complete cardiac catheterization was carried out (Jan. 17, 1947) and blood samples and pressure tracings were taken from the pulmonary artery, its right and left branches, the lower portion of the right ventricle, the right atrium, and the superior and inferior venae cavae (Fig. 2). To rule out the possibility of a high ventricular septal defect, the catheter tip was then advanced from the right atrium into a position supposedly in the conus arteriosus of the right ventricle, and blood was drawn for analysis. Instead of a higher oxygen content than the other ventricular, atrial, and vena caval samples, this blood showed an exceptionally low value inconsistent with the others and quite out of the normal range (Table I). On this occasion the true position of the catheter in the coronary sinus was not known during the procedure but was suspected when the blood analysis revealed the low oxygen content. Thereafter, the entrance of the catheter into the coronary sinus was recognized as it occurred during fluoroscopy.

CASE 3.—A 26-year-old man entered the hospital for study of mild essential hypertension. Three and one-half years previously he had undergone a limited bilateral lumbodorsal sympathectomy (Smithwick). At the time of this study (Feb. 4, 1947) the heart was normal in size by radiographic measurement, the electrocardiogram was interpreted as being within normal limits, and the sphygmomanometric arterial pressure was 140-155/95-110. In the course of

TABLE I. BLOOD OXYGEN AND CARDIAC OUTPUT DATA

	CASE 1 (NORMAL)	CASE 2 (PATENT DUCTUS)		CASE 3 (HYPERTENSION)	CASE 4 (PATENT DUCTUS)	
Coronary venous blood						
O_2 content, ml. per l.	60.4	38.0		87.6	42.5	
O_2Hb content, ml. per l.	60.0	37.6		87.0	42.1	
O_2Hb sat., per cent	31.4	22.6		41.1	25.8	
Arteriovenous O_2 diff., ml. per l.	123.2	117.6		116.5	112.5	
Mixed venous blood Source		RIGHT VENTRICLE	PULMONARY ARTERY	RIGHT VENTRICLE	RIGHT VENTRICLE	PULMONARY ARTERY
O_2 content, ml. per l.	Not obtained	113.5	130.9	161.6	100.0	111.4
O_2Hb content, ml. per l.		112.5	129.9	160.6	99.1	110.5
O_2Hb sat., per cent		67.8	78.2	76.0	60.7	67.7
Arteriovenous O_2 diff., ml. per l.		42.1	24.7	42.5	55.0	43.6
Arterial blood						
O_2 content, ml. per l.	183.6	155.6		204.1	155.0	
O_2Hb content, ml. per l.	181.2	153.2		201.7	152.6	
O_2Hb sat., per cent	95.0	92.3		95.3	93.6	
O_2Hb capacity of blood, ml. per l.	190.9	166.0		211.7	163.1	
Resp. O_2 uptake, ml. per min.	208	222		216	345	
Cardiac output, liters per min. (= resp. O_2 uptake ÷ A-V O_2 diff. of mixed venous blood)	Not determined	5.27 (Systemic circuit)	9.00 (Pulmonary circuit)	5.08	6.28 (Systemic circuit)	7.92 (Pulmonary circuit)
False cardiac output based on coronary A-V O_2 diff., liters per min.	1.69	1.89 (64.2 per cent error)		1.85 (63.6 per cent error)	3.06 (51.3 per cent error)	

a cardiac catheterization performed for the estimation of cardiac output, the tip was placed in the coronary sinus, where its position was recognized, and pressure tracings (Fig. 3) and blood samples (Table I) were taken.

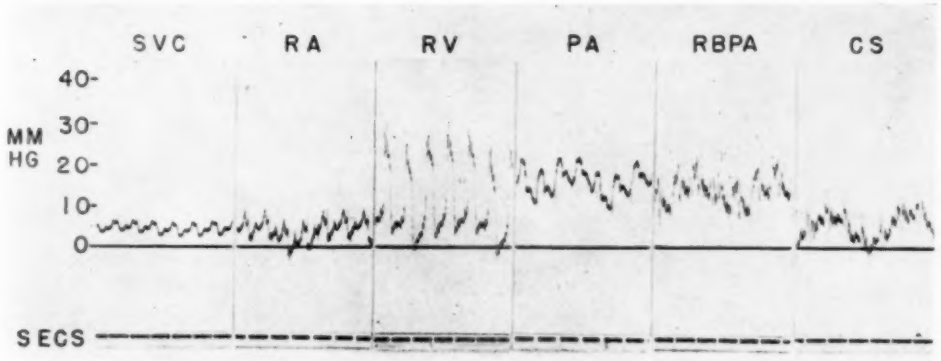


Fig. 2.—Slow optical records of pressures obtained with the catheter tip at various sites in Case 2. *SVC*, superior vena cava. *RA*, right atrium. *RV*, right ventricle. *PA*, pulmonary artery. *RBPA*, right branch of pulmonary artery. *CS*, coronary sinus. Note the mechanical disturbances produced by ventricular systole.

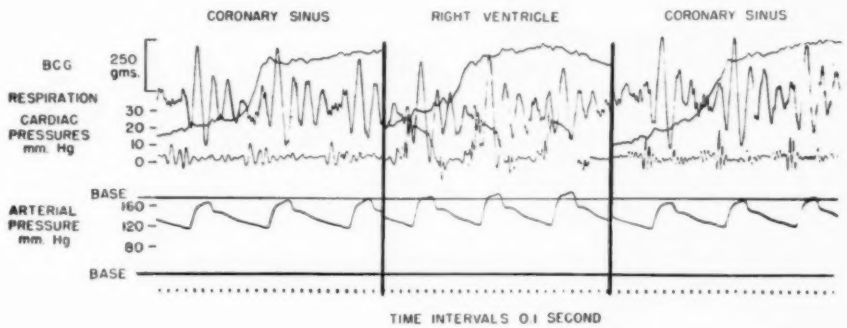


Fig. 3.—Optical records from Case 3. Coronary sinus tracings arranged for comparison with right ventricular pulse waves. Notations as in Fig. 1.

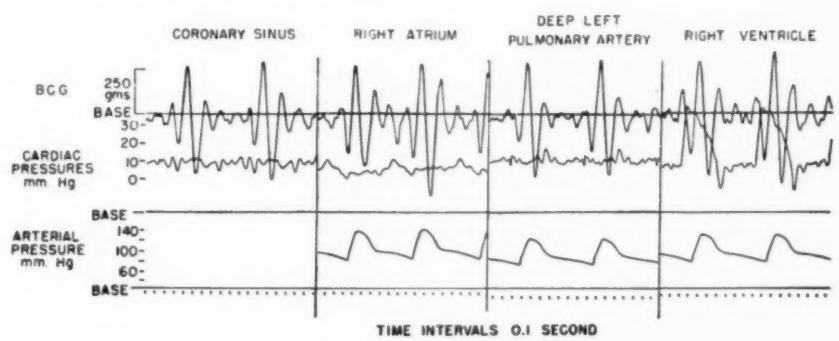


Fig. 4.—Optical records from Case 4. Coronary sinus tracing arranged for comparison with those from the right atrium and ventricle, and one taken from a small distal branch of the pulmonary artery in the left lung. Notations as in Fig. 1.

CASE 4.—A 15-year-old boy entered the hospital for diagnostic studies of congenital heart disease. The heart by x-ray study was within normal limits of size and shape except for moderate prominence of the right atrial and ventricular shadows. There was a loud systolic and a questionable early diastolic murmur over the base of the heart, and the sphygmomanometric blood pressure was 130/80. At the beginning of a diagnostic cardiac catheterization (March 7, 1947) the tip entered the coronary sinus, where pressure tracings (Fig. 4) and blood samples (Table I) were taken. During the subsequent catheter exploration, evidence was obtained indicating the presence of a patent ductus arteriosus and moderate pulmonary stenosis.

SIGNS OF CATHETERIZATION OF THE CORONARY SINUS

1. *Fluoroscopic Appearance.*—The characteristic behavior of the catheter tip under fluoroscopic visualization after entering the coronary sinus was one of the most helpful signs in determining its true position in that venous channel or one of its tributaries. In an ordinary cardiac catheterization the catheter is thrust smoothly ahead until its gently curved tip lies in the right atrium.

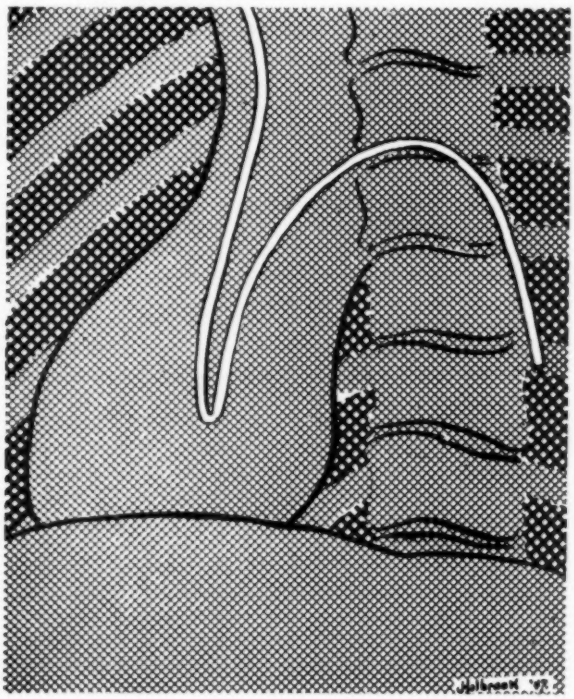


Fig. 5.—Diagram of a spot roentgenogram taken to show the left anterior oblique fluoroscopic view of the heart in Case 4 with the catheter in the left branch of the pulmonary artery. When the catheter tip was advanced farther downward and outward into the pulmonary field, highly oxygenated pulmonary "capillary" blood was obtained.

The tip then is passed toward the left and downward through the atrioventricular orifice until it reaches the diaphragmatic or apical wall of the right ventricle and is deflected upward toward the pulmonary semilunar valves. It then can be passed without resistance into the pulmonary artery (Fig. 5). By contrast,

whenever the catheter tip was passed from the atrium into the orifice of the coronary sinus, which is situated on the atrial septum just posterior to the tricuspid ostium and anterior to the rudimentary valve of the inferior vena cava, it moved immediately to the left and upward in an oblique direction along the coronary sulcus, or atrioventricular groove (Fig. 6). It encountered considerable resistance as it approached the left border of the cardiac silhouette and, if forced, failed to advance but caused the portion of the catheter within the atrium to buckle and form a loop. If it was withdrawn a few centimeters and advanced again, it followed exactly the same course repeatedly. To change its direction one had to withdraw the tip completely into the atrium and seek another route.

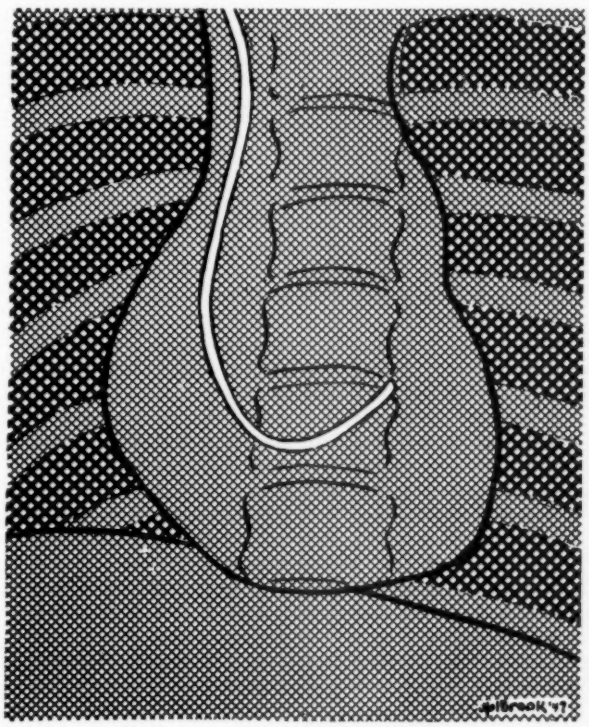


Fig. 6.—Diagram of a spot roentgenogram taken to show the posteroanterior view of the heart in Case 4 with the catheter in the coronary sinus.

2. *Oxyhemoglobin Saturation of Coronary Sinus Blood.*—The second characteristic sign of catheterization of the coronary sinus was the low oxyhemoglobin saturation of the blood obtained through the catheter. This was immediately recognizable grossly from the markedly dark color of the blood as it was withdrawn into the syringe, exceeding that obtainable from any other site in subjects at rest.

On analysis in the Van Slyke apparatus, the oxygen content of these samples of coronary venous blood was found to be extraordinarily low, while the arterio-

venous oxygen difference was correspondingly high (Table I). Thus, in the four cases here reported the oxyhemoglobin saturation of the coronary sinus blood was 31, 23, 41, and 26 per cent and the arteriovenous oxygen difference was 12.3, 11.8, 11.7, and 11.3 volumes per cent, respectively. These values are in striking contrast with the mean oxyhemoglobin saturation of 73 (standard deviation ± 4.3) per cent and the average arteriovenous oxygen difference of 4.05 (standard deviation ±0.65) volumes per cent in samples of mixed venous blood obtained in this laboratory from the pulmonary artery or right ventricle of fifty normotensive or hypertensive patients without cardiac failure and at rest (Fig. 7). The markedly greater range of the values for oxyhemoglobin saturation as compared with arteriovenous oxygen difference of the coronary venous samples in these four cases is explained by their differences in oxyhemoglobin capacity (Table I).

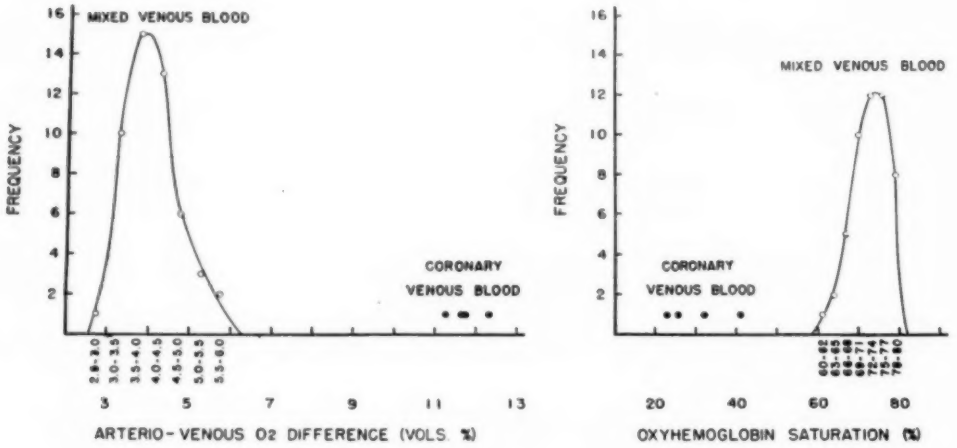


Fig. 7.—Charts illustrating comparative values and frequency distributions of the oxyhemoglobin saturation and the arteriovenous oxygen difference of coronary venous blood (in four cases) and of mixed venous systemic blood (in fifty normotensive and hypertensive subjects at rest and without cardiac failure).

3. *Blood Pressure Within the Coronary Sinus.*—The third sign which was helpful in identifying the position of the catheter tip within the coronary sinus was the character of the pressure tracings obtained with the Hamilton manometer. The pressures recorded from the sinus were usually low (0 to 15 mm. Hg) and varied rhythmically with respiration (Figs. 1 and 2). In this respect they resembled tracings obtained with the tip in the atrium, but they were dissimilar in that they ranged slightly higher and did not show the characteristic auricular pulses (Fig. 4). Instead, they usually were marked by three series of waves or vibrations, the *first* and smallest of which appeared with the atrial contraction and frequently continued to the *second* series, with ventricular contraction, while the *third* appeared with or just after the peripheral arterial pulse (Figs. 1, 3, and 4). These vibrations usually bore little resemblance to the larger, more sustained systolic pressure waves recorded from the right ventricle or the pulmonary artery. However, in Case 1 (Fig. 1), in which the catheter tip undoubtedly was advanced

farther into a coronary vein than in any of the others, there were at times definite sustained waves which at first glance did resemble those seen in tracings from the ventricle or pulmonary artery, but upon careful analysis were found to occur at the time of the third group of vibrations described earlier in this paragraph, synchronously with, or just following, the peripheral arterial (femoral) pulse waves. Hence, they occurred in the *diastolic* phase of the heart's action and therefore were considered, along with the third series of vibrations, to be possibly the result of a sudden increase in coronary blood flow early during diastole.

Thus, four types of variations were found in coronary sinus pressure: respiratory, atrial, ventricular, and "coronary." They varied in size and somewhat in shape, not only in the different subjects but also in the same subject with slight changes of position of the catheter tip within the sinus, and even from time to time without any apparent change in position (Figs. 1 and 3). Some of these variations undoubtedly were due to greater and lesser amounts of mechanical artefacts set up in the catheter by its movement with the heart beats. Some changes, especially in the amplitude and duration of the "coronary" waves, apparently depended upon the relative completeness with which the catheter occluded the coronary sinus or a tributary vein. However, except in Case 1, the absence of well-defined, sustained wave forms resembling those obtained in the ventricle was a characteristic and helpful sign in identifying the true position of the tip when it appeared during fluoroscopy to be possibly in the pulmonary conus. The only other situation beyond the atrium where low pressures and minimal pulse waves were recorded was deep in a branch of the pulmonary artery (Fig. 4), from which a sample of blood could be seen immediately to be highly oxygenated. Moreover, this position was easily identifiable by an anterior oblique fluoroscopic view and occasioned no difficulty during catheterization (Fig. 5). This source of oxygen-saturated pulmonary "capillary" blood has been noted and described by Dexter and associates.[5]

DISCUSSION

Sosman and Dexter[6] have recognized accidental catheterization of the coronary venous system in two cases and in one of them reported the pressure to be 12 mm. Hg, the oxygen content of the blood, 7.4 volumes per cent, and its saturation, 25 per cent. These values are within the ranges of the observations here reported in four additional cases. In both groups the relative ease and apparent harmlessness of catheterization of the human coronary sinus has suggested its applicability for a wide variety of possible studies on coronary blood flow and cardiac metabolism in man. There seems little doubt that if the coronary sinus can be entered fortuitously in 16 per cent of cases, it can be catheterized deliberately in a majority of cases.*

From these observations one can state, furthermore, that in a subject at rest the degree of oxygen extraction by the myocardium from coronary blood is remarkably near complete. It follows that any considerable increase in demand by the myocardium for oxygen under conditions of exercise must be met by

*Since the presentation of this paper such studies have been undertaken elsewhere.[7,8,9]

increased coronary blood flow rather than by increased oxygen extraction. These findings in man are consistent with those reported previously by others[10,11] for the dog. Moreover, it would seem that attempts to increase the oxygen extraction by means of certain enzymic preparations are relatively unpromising. However, the technique of coronary sinus catheterization should be applicable to the solution of this problem.*

The results of this study have emphasized a major source of error in sampling mixed venous blood, as required for the determination of cardiac output by the direct Fick method. If the tip of the catheter is placed in the coronary sinus but presumed to be in the right ventricle and the oxygen content of the blood withdrawn therefrom is used in calculating the cardiac output, the resulting values are greatly in error, being less than one-half the actual cardiac output (Table I). Even if the tip of the catheter is within the atrial chamber but near the coronary orifice or in the stream of blood issuing from it, an admixture of coronary venous blood with the atrial sample may occur. In order to be certain of obtaining thoroughly mixed systemic venous blood, one should place the tip of the catheter in the pulmonary artery or the proximal portion of its right or left branch. Another distinct advantage of this practice is that it enables one to withdraw the blood in a smooth, continuous stream because of the well-sustained pulmonary arterial diastolic pressure. In the right ventricle, where the diastolic pressure approaches or falls to zero, sampling is sometimes difficult (Figs. 2, 3, and 4).

As yet, insufficient data have been collected concerning the pressure relationships in various portions of the coronary venous system. It appears that in the sinus itself the pressures are relatively low, reflecting its continuity with the atrium, and are characterized usually by minor variations due to respiratory and cardiac movements. Farther out in the system, however, there may occur in early diastole sustained waves which possibly reflect the increase in coronary blood flow at that time. It will be of interest to follow the further accumulation of data on these points.

SUMMARY

An intravenous catheter was introduced inadvertently into the coronary sinuses of four patients in the course of a series of twenty-five cardiac catheterization studies (a frequency of 16 per cent). Samples of coronary venous blood were taken for oxygen analysis, and pressure tracings were obtained with a Hamilton manometer. These cases are reported and criteria for identifying this catheter position are presented.

Oxyhemoglobin saturation values were found to be strikingly low (average, 30 per cent in four cases) as compared with control values for mixed venous blood (average, 73 per cent in fifty subjects). Coronary venous pressure levels (0 to 15 mm. Hg) and wave patterns are described. Physiologic implications of the findings and potential applications of the technique are cited.

*As this paper was being submitted for publication, a preliminary report appeared[12] indicating that in dogs breathing low oxygen mixtures the intravenous injection of cytochrome C did not increase the removal of oxygen from the coronary blood.

The authors gratefully acknowledge the technical assistance of Mrs. Gloria Kligler, B.A., Miss Gretchen Baum, B.S., Miss Martha Hanson, A.B., and Miss Adele Rymut, A.B.; and they wish to thank Miss Jane Holbrook, A.B., for preparing the diagrams and photographic reproductions.

REFERENCES

1. Cournand, A., Riley, R. L., Breed, E. S., Baldwin, E. deF., and Richards, D. W., Jr.: Measurement of Cardiac Output in Man Using the Technique of Catheterization of the Right Auricle or Ventricle, J. Clin. Investigation **24**:106, 1945.
2. Hamilton, W. F., Brewer, G., and Brotman, I.: Pressure Pulse Contours in the Intact Animal. I. Analytic Description of a New High Frequency Hypodermic Manometer With Illustrative Curves of Simultaneous Arterial and Intracardiac Pressures, Am. J. Physiol. **107**:427, 1934.
3. Wilkins, R. W.: A Tilting Ballistocardiograph, Am. Heart J. **26**:351, 1943.
4. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement. I., J. Biol. Chem. **61**:523, 1924.
5. Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Sagerson, R. P., and Evans, J. M.: Studies of Congenital Heart Disease. II. The Pressure and Oxygen Content of Blood in the Right Auricle, Right Ventricle, and Pulmonary Artery in Control Patients, With Observations on the Oxygen Saturation and Source of Pulmonary "Capillary" Blood, J. Clin. Investigation **26**:554, 1947.
6. Sosman, M. C., and Dexter, L.: Venous Catheterization of the Heart, Radiology **48**:441, 1947.
7. Eckenhoff, J. E., Hafkenschiel, J. H., Harmel, M. H., Goodale, W. T., Lubin, M., Bing, R. J., and Kety, S. S.: The Measurement of Coronary Blood Flow by the Nitrous Oxide Method, Am. J. M. Sc. **214**:693, 1947.
8. Goodale, W. T., Lubin, M., and Banfield, W. G., Jr.: Catheterization of the Coronary Sinus, Am. J. M. Sc. **214**:694, 1947.
9. Bing, R. J., Vandam, L. D., Gregoire, F., Handelsman, J. C., Goodale, W. T., and Eckenhoff, J. E.: Catheterization of the Coronary Sinus and the Middle Cardiac Vein in Man, Proc. Soc. Exper. Biol. & Med. **66**:239, 1947.
10. Eckenhoff, J. E., and Landmesser, C. M.: Direct Measurement of Coronary Blood Flow in the Anesthetized Dog, Am. J. M. Sc. **212**:123, 1946.
11. Eckenhoff, J. E., Hafkenschiel, J. H., and Landmesser, C. M.: The Oxygen Metabolism of the Dog's Heart, Am. J. M. Sc. **213**:123, 1947.
12. Hafkenschiel, J. H., and Eckenhoff, J. E.: The Oxygen Content of Coronary Venous Blood as Affected by Anoxia and Cytochrome C, Fed. Proc. **7**:224, 1948.

A SIMPLE BIPOLAR TECHNIQUE FOR THE ANALYSIS OF THE VECTOR RELATIONSHIP BETWEEN THE UNIPOLAR AND STANDARD ELECTROCARDIOGRAPHIC LEADS

NATHANIEL A. COHEN, M.D., AND A. M. GLICKSMAN, M.A.
FOREST HILLS, N. Y.

IN 1934 Wilson[1] suggested the use of an indifferent electrode of zero potential which would make it possible to determine the potential variations at a single point on the surface of the body without reference to changes in potential at any other point. Goldberger[2] in 1942 demonstrated that electrocardiograms of similar wave form, but larger by one-half than Wilson's, could be obtained by means of an indifferent electrode consisting of two electrodes connected to a common terminal attached to the extremities not being "explored" and eliminating Wilson's 5,000 ohm resistors.

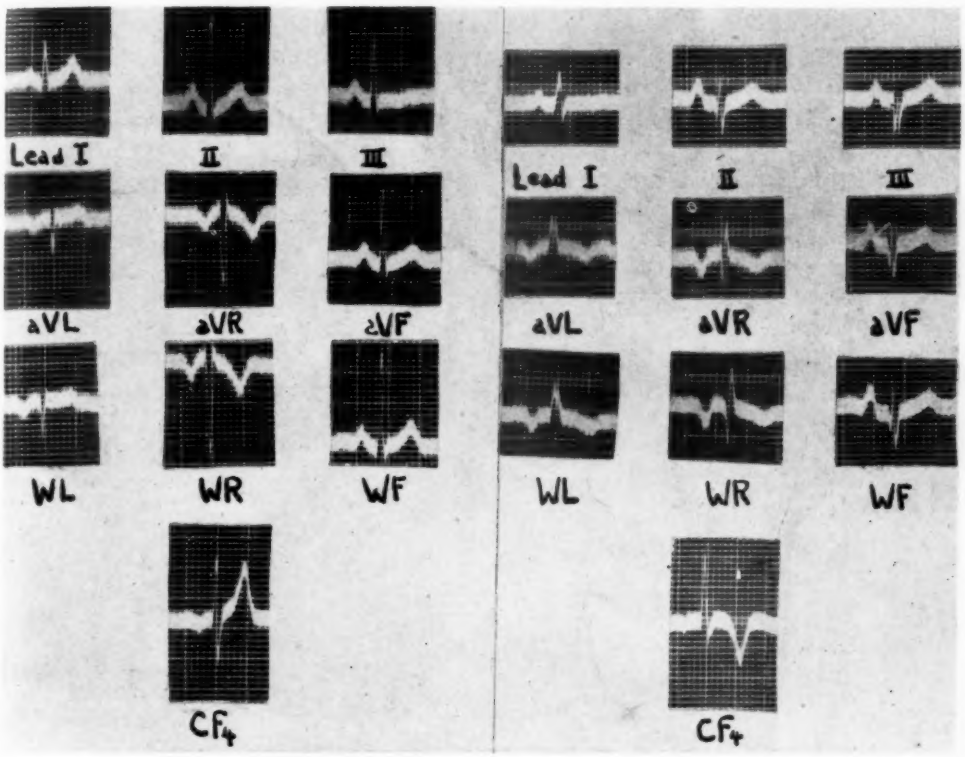
It is the purpose of this paper to demonstrate that electrocardiograms of wave form similar to the unipolar electrocardiograms can be obtained by simple bipolar leads and that this establishes the vector relationship between the unipolar and standard leads.

METHOD

The following method of taking electrocardiograms was used. The positive or "exploring" electrode was placed on the left arm and the negative or indifferent electrode at a point in the midaxillary line halfway between the apex of the right axilla and the symphysis pubis. The distance from the apex of the axilla to the pubis was measured with a tape, the distance halved, and with the end of the tape in the axilla, the other end of the tape was swung laterally so that it came to lie along the midaxillary line, its midpoint being "diametrically" opposite the extremity being "explored." A tracing was obtained which was similar in form to the unipolar left arm leads but which was twice as large as Wilson's and one-third again as large as Goldberger's. For convenience of designation, this lead was called W_L. Lead W_R is written in a similar manner, the "exploring" electrode being placed on the right arm and the negative electrode at the halfway point in the left midaxillary line. Lead W_F is obtained by the positive electrode being placed on the left leg and the negative electrode on the submental fat pad.

The bipolar electrocardiograms designated as "W" leads (Fig. 1) are presented for comparison with the augmented unipolar limb leads. The first is from a normal individual and the second from an individual who had an old anterior wall infarction.

From the Medical Unit, New York Regional Office Clinic, Veterans Administration.
Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.



A. *B.*

Fig. 1. Electrocardiograms showing the similarity in wave form between the augmented unipolar leads and the W or bipolar unipolar-type leads. *A*, Normal; *B*, old anterior wall infarction.

DISCUSSION

This method is not recommended for clinical use since it is based on the assumption that the heart is centrally situated and that the point midway between axilla and pubis is diametrically opposite the "explored" extremity. However, in an emergency, by the simple expedient of standardizing the electrocardiograph so that 1.0 mv. is equivalent to 0.5 cm., a reasonable facsimile of Wilson's leads can be obtained using a single pair of electrodes.

The following solution is offered. If for theoretical considerations the body is considered as an ovoid with an electrical dipole near its center which is surrounded by a uniformly conducting medium, then the potential V_L measured by an electrode at any point L on its surface, can be described by the equation $V_L = \frac{K \, Cos \, \theta}{r_1^2}$, where K is a constant and r_1 is the distance between the electrode and the center of the dipole and θ represents the angle between a line drawn from the center of the dipole and the electrode at L and a line drawn in the direction of the electrical axis of the dipole.[3] (See Fig. 2.)

The potential at W can be described by the equation $V_W = \frac{K\ Cos\ (180 - \theta)}{r_2^2}$ where r_2 is the distance from the center of the dipole and a point W which is diametrically opposite L.

$$\text{Then} \quad V_L - V_W = \frac{K\ Cos\ \theta}{r_1^2} - \frac{K\ Cos\ (180 - \theta)}{r_2^2}$$

$$\text{Since} \quad \frac{K\ Cos\ (180 - \theta)}{r_2^2} = -\frac{K\ Cos\ \theta}{r_2^2}$$

$$\text{Then} \quad V_L - V_W = \frac{K\ Cos\ \theta}{r_1^2} + \frac{K\ Cos\ \theta}{r_2^2}$$

$$= \frac{K\ Cos\ \theta}{r_1^2}\left(1 + \frac{r_1^2}{r_2^2}\right)$$

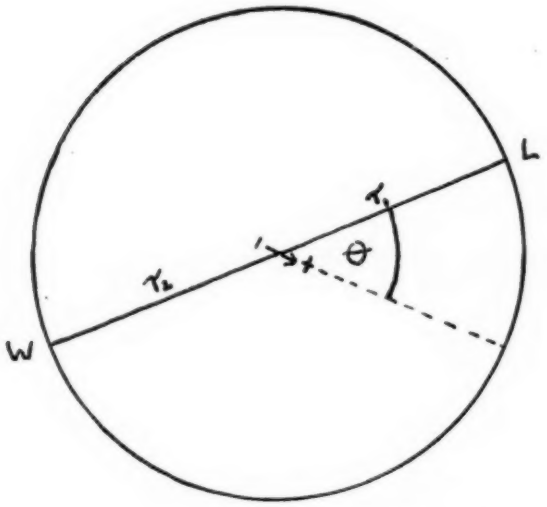


Fig. 2. The mathematical relationship between diametrically opposed electrodes and the electrical axis of the heart.

This formula is applicable to any figure which has central symmetry. For a sphere, $r_1 = r_2$ for every point L,

$$\text{Therefore} \quad V_L - V_W = \frac{2\ K\ Cos\ \theta}{r^2}$$

Since the difference in potential at L and an indifferent electrode of zero potential T may be described:

$$V_L - V_T = \frac{K\ Cos\ \theta}{r^2}$$

then

$$V_L - V_W = {}_2\ (V_L - V_T)$$

Also for a sphere, since $r_1 = r_2$, then $V_L = -V_W$

Expressed qualitatively, this is equivalent to saying that whereas Wilson derives the potential at a single extremity by the use of an indifferent electrode of zero potential, by the method described by the authors the potential variation at a single extremity may be written by tapping the potential at that extremity and its simultaneous equal and opposite variation. For example, if by Wilson's method a potential of 4.0 mv. be obtained, then by the method described by the authors one would obtain a deflection equivalent to 8.0 mv., since $V_L - V_W = 4 - (-4)$ or 8, and the wave form of the electrocardiograms must be the same although varying in amplitude by twice. (See Fig. 3.)

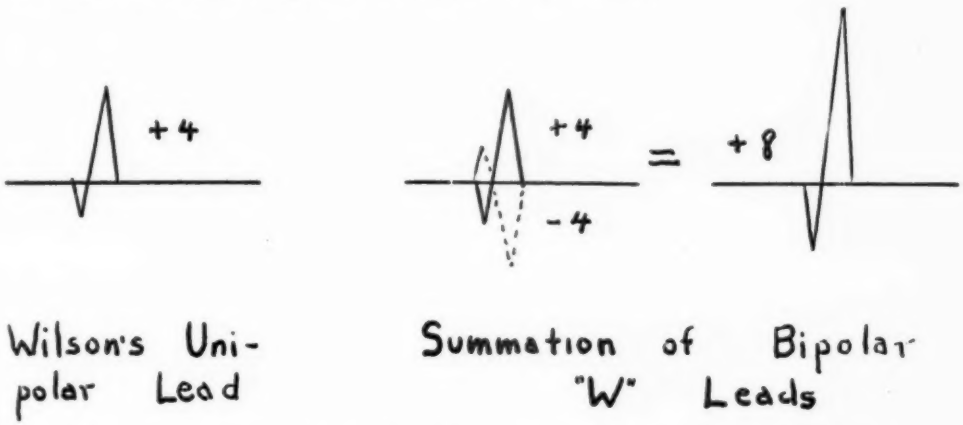


Fig. 3.—Diagrammatic representation of the summation of mirror image waves of similar form and opposite sign in bipolar unipolar-type W leads.

It is suggested that the Goldberger augmented unipolar limb leads are unipolar in the sense that the wave inscribed has similar form to Wilson's, but they actually do not employ an indifferent electrode of zero potential but rather one which measures a simultaneous quantity of opposite sign, one-half the magnitude of the Wilson unipolar lead, the summation of which gives a wave of similar form three-halves the magnitude of Wilson's. This is apparent from Goldberger's[4] explanation for the augmentation of his unipolar leads in which he indicates that the augmented unipolar limb leads actually represent the difference in potential between the unipolar potential of the right arm, for example, and the mean potential of the other extremities, or:

$$\text{Augmented potential of right arm} = RA - \frac{LA + LL}{2}$$

$$\text{Since} \quad RA + LA + LL = 0$$

$$\text{and} \quad LA + LL = -RA$$

$$\text{then} \quad \frac{LA + LL}{2} = -\frac{RA}{2}$$

$$\text{or augmented potential of right arm} = RA - \left(-\frac{RA}{2}\right)$$

$$= 3/2\, RA$$

If the mean potential of the other extremities, $\frac{LA + LL}{2}$, is equal to one-half the potential at the right arm, $-\frac{RA}{2}$, it cannot at the same time be equal to zero (see Fig. 4.).

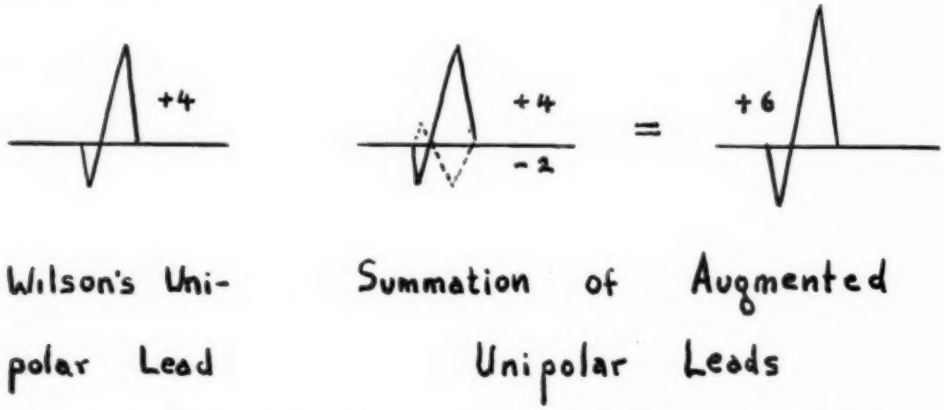


Fig. 4.—Summation of positive deflection and its half-sized negative counterpart of similar form resulting in the augmented unipolar lead.

The importance of W leads is that they demonstrate that waves similar to the unipolar leads can be obtained by bipolar leads, indicating that the unipolar leads, both Wilson's and Goldberger's, represent the resolution of vectors having the same direction as the W leads. Therefore, the unipolar leads not only "resemble" the standard leads but may be thought of as being related to the standard leads by rotation of the "indifferent" or negative electrode through an arc of 30°. The unipolar leads, therefore, as much represent the vectors passing through the heart as the standard leads represent forces passing tangentially to the heart (Fig. 5).

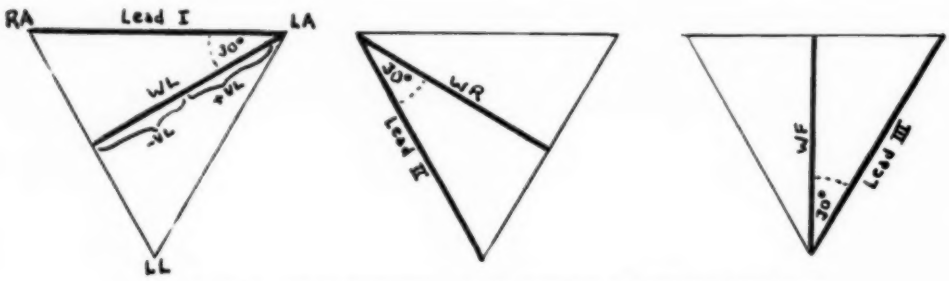


Fig. 5.—The vector relationships of the standard and unipolar limb leads.

It is of interest that the method of bipolar unipolar-type leads is not subject to the limitation of assuming that the electrical axis of the heart lies in the plane of Einthoven's triangle. In the above derivation, orientation of the axis of the heart is immaterial so long as points opposite are employed. This may have

particular significance in elucidating some of the minor discrepancies in the precordial unipolar tracings in bundle branch block.[5]

The experiment with bipolar diametrically opposed leads was independently conceived by the authors but clearly anticipated by Wilson[6] in a recent article in which he states, "If the cardiac field at points far distant from the heart is nearly equivalent to that of a doublet, leads from two points equidistant from this organ and at opposite ends of a line which passes through its center should yield complexes exactly opposite in character if the leads employed are unipolar."

SUMMARY

1. A method of obtaining unipolar-type leads with simple bipolar diametrically opposed electrodes is presented.

2. The unipolar leads may be considered as radius vectors related to the standard leads through an arc of 30°.

The authors wish to express appreciation to Dr. Morris Lattman, Chief, Cardiac Clinic, New York Regional Office Clinic, Veterans Administration, to Dr. Milton Mendlowitz, and to Mr. Walter A. Brecher for helpful suggestions and technical assistance.

REFERENCES

1. Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Electrocardiograms That Represent the Potential Variations of a Single Electrode, Am. Heart J. **9**:477, 1934.
2. Goldberger, E.: A Simple Electrocardiographic Electrode of Zero Potential and a Technic of Obtaining Augmented Unipolar Extremity Leads, Am. Heart J. **23**:483, 1942.
3. Goldberger, E.: Unipolar Lead Electrocardiography, Philadelphia, 1947, Lea & Febiger, p. 16.
4. Goldberger, E.: Unipolar Lead Electrocardiography, Philadelphia, 1947, Lea & Febiger, p. 55
5. Wolferth, C. C., and Livezy, M.: A Study of Methods of Making So-Called Unipolar Electrocardiograms, Am. Heart J. **27**:764, 1944.
6. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., and Barker, P. S.: On Einthoven's Triangle, the Theory of Unipolar Electrocardiographic Leads and the Interpretation of the Precordial Electrocardiogram, Am. Heart J. **32**:277, 1946.

Clinical Reports

OBSTRUCTIONS OF THE SUPERIOR VENA CAVA

A Review of the Literature With Two Case Reports

David B. Hinshaw, M.D.
Glendale, Calif.

THE clinical picture of obstruction of the superior vena cava is a symptom complex and not a specific disease entity. Many papers, case reports, and discussions of various aspects of obstruction of the superior vena cava have appeared in medical literature over a period of many years, but it is difficult to find a brief summary of well-established criteria for diagnosis, prognosis, and therapy.

The purpose of this present paper is threefold: (1) to review the essential points of the literature since 1934; (2) to report two additional cases of obstruction of the superior vena cava, one of particular interest; and (3) to summarize in one place the major points of diagnosis and treatment as related to this unusual syndrome.

REVIEW OF THE LITERATURE

In 1934 Ehrlich, Ballon, and Graham[1] published a detailed review of the literature up to that time, a total of 309 cases.

Some general observations can be made regarding signs and symptoms. When obstruction of the superior vena cava has occurred, the symptoms and findings are essentially alike, regardless of the etiology. The clinical picture of obstruction is usually preceded by or accompanied by other signs and symptoms related to the factor causing the caval obstruction (bronchogenic carcinoma, for example), except when the etiological factor happens to be an intraluminal obstruction (primary thrombus) or a long-standing, otherwise asymptomatic fibrotic process in the mediastinum. In general, then, the early symptoms of cases of obstruction of the superior vena cava will be those of the causative disease concerned. Later in this paper the signs and symptoms of obstruction of the superior vena cava will be described in sufficient detail to facilitate the adequate diagnosis of this condition.

From the Department of Medicine of the College of Medical Evangelists and the White Memorial Hospital, Los Angeles, Calif.

A review of the literature from April, 1934, to Jan. 1, 1947, revealed a total of 125 reported cases which present unquestionably the clinical syndrome of obstruction of the superior vena cava. Several case reports have appeared which were not included in this review because the clinical descriptions were inadequate to support a diagnosis of complete obstruction of the superior vena cava. Hussey[2] reported fifty-two cases of venous compression in the mediastinum with venous pressure studies. Hussey's paper was a study of venous pressure dynamics in various lesions affecting the innominate and subclavian vessels as well as the superior vena cava. The majority of these cases were not described in sufficient detail to make it possible to classify them in this study; consequently, they were excluded. Pilcher and Overholt[3] reported fifty cases of venous obstruction in the upper mediastinum. A large number of these were attributed to intrathoracic goiter. The diagnoses were based chiefly on elevated venous pressures in the upper extremities, frequently below 200 mm. H_2O, while the classical clinical picture of obstruction of the superior vena cava was not described clearly in most of the instances. Therefore, only a small percentage of these cases were included. Three foreign papers with a total of five cases were not available for this study.

The 125 cases which have been collected are classified on the basis of their etiology as follows: (1) carcinoma of the bronchus with metastasis to the mediastinal nodes, twenty cases (16 per cent)[4-10]; (2) metastatic carcinoma other than bronchogenic, nine cases (7.2 per cent)[4,5,11,12]; (3) lymphoblastomas (including Hodgkin's disease), fifteen cases (12 per cent)[4,5,11,13,14]; (4) primary mediastinal tumors, four cases (3.2 per cent)[4,15]; (5) aortic aneurysms (almost all syphilitic), twenty-nine cases (23.2 per cent)[4,5,6,11,14,16-28]; (6) mediastinitis, five cases (4 per cent)[14,29,30]; (7) "mediastinal fibrosis" (chronic mediastinitis of undetermined type with scar tissue formation, constricting bands, and other similar changes, eleven cases (8.8 per cent)[4,31,32,33]; (8) thrombosis (excluding those secondary to invasion by malignant tumors), seventeen cases (13.6 per cent)[34-46] (eight of these cases were considered to be idiopathic or primary thrombosis); and (9) miscellaneous causes, fifteen cases (12 per cent)[4,5,47,48,49] (see Table 1).

Numerous instances of thrombosis of the superior vena cava are on record in which the thrombotic process was the direct result of invasion of the vein proper by malignant tumor tissue. Seventeen patients (13.6 per cent) of this group had thrombosis from other factors; since these cases are quite rare, they should be noted in some detail. In eight of the seventeen cases thrombosis was apparently primary. In the other nine cases thrombosis was thought to be secondary: in three cases thrombosis was associated with pulmonary tuberculosis; in two, with septicemia; in two thrombosis was alleged to be due to thrombophlebitis; in one it was attributed to nicotine sensitivity; and in one thrombosis was secondary to right auricular thrombosis following Bernheim's syndrome.[42] The incidence of thrombosis of the superior vena cava here recorded is considerably greater than that reported by Ehrlich, Ballon, and Graham[1] in 1934. A detailed study of thrombosis of the superior vena cava alone was published by Ochsner and Dixon in 1936.[34]

TABLE I. ETIOLOGY OF OBSTRUCTION OF SUPERIOR VENA CAVA IN 125 CASES REPORTED IN THE LITERATURE BETWEEN APRIL, 1934, and JANUARY, 1947

	CAUSE	CASES	PER CENT OF TOTAL
I	Carcinoma of the bronchus (bronchogenic) with mediastinal metastasis	20	16
II	Lymphoblastomas (including Hodgkin's disease)	15	12
III	Aortic aneurysm (syphilitic)	29	23.2 (total)
	(a) Due to *pressure* from aneurysm 14 cases (11.2%)		
	(b) Rupture into superior vena cava[5,17-27] 14 cases (11.2%)		
	(c) Dissecting aneurysm (arteriosclerotic)[28] 1 case (0.8%)		
IV	Metastatic carcinoma to mediastinum (excluding bronchogenic)	9	7.2 (total)
	(a) Carcinoma of thyroid 4 cases (3.2%)		
	(b) Others from various sources		
V	Primary mediastinal tumors (two of these were considered to be malignant tumors)	4	3.2
VI	Mediastinitis	5	4 (total)
	(a) Tuberculosis 2 cases (1.6%)		
	(b) Syphilitic 2 cases (1.6%)		
	(c) Pyogenic 1 case (0.8%)		
VII	"Mediastinal fibrosis"	11	8.8
VIII	Thrombosis of superior vena cava (excluding those cases due to invasion of the vein by malignant tumors)	17	13.6
IX	Miscellaneous causes	15	12.0 (total)
	(a) Undetermined (so classified by those who reported them)		
	1. Mediastinal mass present 4 cases (3.2%)		
	2. No medistinal mass 4 cases (3.2%)		
	(b) Acute leucemia (lymphocytic) 3 cases (2.4%)		
	(c) Pericardial constriction (pericarditis) 2 cases (1.6%)		
	(d) Pneumothorax (2-month-old infant) 1 case (0.8%)		
	(e) Mitral stenosis—left auricular dilitation and superior vena caval compression 1 case (0.8%)		
		125 (Total)	100 (Total)

Among the group of cases under the heading of miscellaneous causes are several of special note. Three cases of obstruction of the superior vena cava have been reported in patients having leucemia. In two of these the obstruction of the superior vena cava was an incidental finding, while in one instance it was the first manifestation of leucemia to be found. This may represent a sarcoma-

tous phase of leucemia involving the mediastinal lymph nodes which surround the superior vena vava. One case of obstruction of the superior vena cava was due to pressure from a greatly dilated left atrium resulting from mitral stenosis.[48] Another unusual situation was that of obstruction due to a spontaneous pneumothorax in a 2-month-old infant.[49]

Aortic aneurysm in its various forms caused obstruction in 23.2 per cent of the cases in this collected series, as compared with 36 per cent in that of Ehrlich, Ballon, and Graham.[1] This is especially interesting in view of the fact that these authors did not include cases due to rupture of the aneurysm into the superior vena cava; this group comprised 11.2 per cent of the total cases in this present series. A complete review of spontaneous thoracic arteriovenous aneurysms reported up to 1938 has been made by Armstrong, Coggin, and Hendrickson.[17]

The incidence of primary malignant thoracic tumors as causative agents is also somewhat higher in the report of Ehrlich, Ballon, and Graham.[1] The group of cases in which obstruction is attributed to "mediastinal fibrosis," including scar tissue, chronic mediastinitis, and other allied disorders, is approximately the same in each series. It is of interest to note that benign goiter practically never causes well-developed obstruction of the superior vena cava.

DIAGNOSIS, TREATMENT, AND PROGNOSIS

The diagnostic clinical criteria of obstruction of the superior vena cava may be outlined as follows:

1. The demonstration of significantly elevated venous pressure (180 mm. H_2O or above) in the upper half of the body in the presence of normal venous pressure in the lower half of the body. This may be determined by the use of the usual venous pressure apparatus or by the observation of unquestionable edema of the upper half of the body with none in the lower extremities.

2. The demonstration of collateral circulation which circumvents the superior vena cava. This includes the observation of visibly dilated veins over the upper half of the body, chiefly the anterior chest. The use of infrared photography frequently outlines this collateral circulation. It may be visualized even better by phlebography.

3. The demonstration by phlebography of the point of obstruction or the demonstration by a roentgenogram of a mass or other lesion which might be considered adequate to cause obstruction of the superior vena cava.

The diagnosis must rest upon objective and not subjective evidence. Any symptom related to the cardiorespiratory system may be experienced by these patients. Cyanosis or deep flushing of the face is frequently seen and patients often complain of a feeling of fullness or congestion in the head and neck, especially after reclining or after stooping.

In the case of rupture of aortic aneurysms into the superior vena cava, the picture is that of acute obstruction. The signs are severe cyanosis, edema, dyspnea, and greatly elevated venous pressure in the upper extremities. Other less diagnostic findings are discussed carefully by Armstrong, Coggin, and Hendrickson.[17]

One author[11] emphasizes that the presence of a disassociation between the venous pressure and the circulation time (arm to tongue) is an important sign in obstruction of the superior vena cava. However, in most reported cases in which both are mentioned, the circulation time was prolonged.

The treatment in obstructions of the superior vena cava must necessarily be directed chiefly to the underlying disease entity. In the lymphomas, for example, radiation therapy is frequently of great help. Under roentgen radiation many large mediastinal masses will melt away, giving at least transitory relief of the venous obstructive symptoms.

In most instances patients with syphilitic mediastinitis should receive antisyphilitic therapy. Pyogenic mediastinitis demands chemotherapy or the use of antibiotics. The use of anticoagulants would be indicated in thrombosis of recent origin; no patients having anticoagulant therapy were found in this review.

There are several instances in which surgical intervention is indicated: (1) rarely, to attempt to remove benign mediastinal tumors; (2) to release fibrous bands and adhesions causing obstruction of the superior vena cava; and (3) to decompress the mediastinum in cases of marked obstruction or when the obstruction is increasing rapidly. This is frequently applicable as a temporary life-saving procedure even when the obstruction is due to malignant tumors.

The prognosis is that of the underlying disease to a large extent. The veins adapt quite well to the obstructive process if the obstruction develops slowly. It has been noted that if the obstruction has occurred below the level of the entry of the azygos vein into the superior vena cava, the venous pressure is higher and the prognosis more serious than if the obstruction is above the entrance of the azygos vein. However, the external evidences of collateral circulation are less marked from the lesions occurring below the entrance of the azygos vein. One patient with aortic aneurysm lived nineteen years after the diagnosis of obstruction was made.[29] The nature of the primary disease is obviously the factor of most importance in the prognosis. Patients tolerate obstruction of the superior vena cava itself surprisingly well and often for long periods of time.

The youngest patient with obstruction of the superior vena cava whose case has been reported was a 2-month-old baby suffering from spontaneous pneumothorax.[49] The oldest patient was a 93-year-old man who had thrombosis of the superior vena cava with extensive collateral circulation.[36]

A total of 434 cases of obstruction of the superior vena cava have been reported up to January, 1947. This number probably does not really reflect the rarity of the syndrome, however, as it is such a dramatic entity that observed cases are likely to have found their way into the literature.

In a review of 85,000 consecutive admissions to the White Memorial Hospital in Los Angeles, Calif., only four examples of this syndrome could be found. This suggests an incidence of approximately one case among 21,250 general hospital admissions. Two of these cases are reported in this paper.

CASE REPORTS

CASE 1.—This patient was a 62-year-old Mexican man who entered the White Memorial Hospital Sept. 20, 1946. For two weeks prior to his admission he had noticed cough, progressive

dyspnea, orthopnea, and edema of the face and upper extremities. For one week prominent anterior thoracic veins had been noted. He had had no edema of the lower extremities or sacrum, no chest pain, and no hemoptysis.

Past history revealed that a chronic, nonproductive cough had been present for several months. A senile type of diabetes mellitus which had apparently been well controlled had been known for twelve years. No important family history could be elicited.

Physical Examination.—On physical examination the patient was seen to be a well-developed, rather obese, elderly Mexican. He was markedly orthopneic and showed extensive edema of the face and upper extremities. Moderate cyanosis of the lips and nail beds was present. The blood pressure was 155/80 bilaterally. The pulse was 96 per minute, the respiration was 32 per minute, and the temperature was normal. His face, especially the eyelids, was so edematous that the eyes were nearly closed. The pupils were equal and reacted to light and accommodation. The ophthalmoscopic examination was normal except for moderate venous engorgement. The

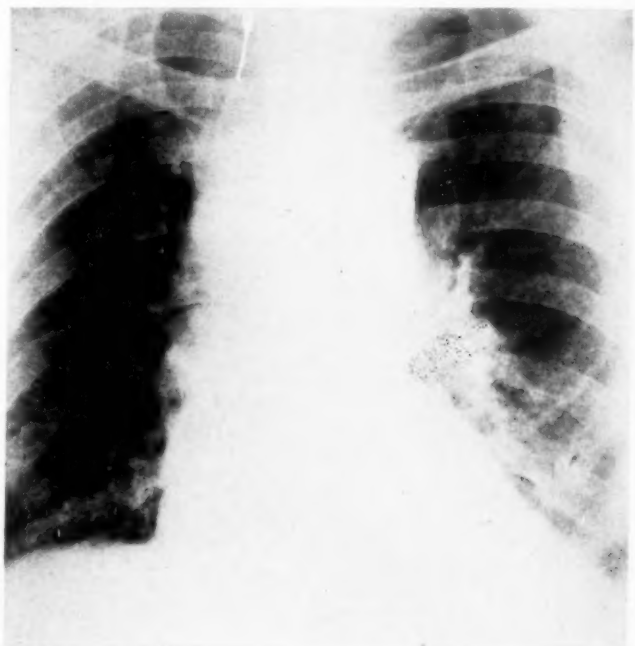


Fig. 1.—Case 1. A roentgenogram of the chest showing mediastinal widening and infiltration in the left base.

ears, nose, and throat were not unusual. The neck was edematous, and markedly engorged veins could be seen. The thyroid gland was not palpable. There were large, dilated, tortuous veins over the entire anterior chest wall. Patches of dilated venules were scattered over the anterior chest and axillae. Impaired resonance to percussion was noted over the left posterior base, with decreased breath sounds and tactile fremitus over this same area. Numerous fine, moist, inspiratory râles were present in the right base, while the apices were clear to auscultation. The heart was not significantly enlarged. A Grade 2, blowing, apical, systolic murmur was present. The aortic second sound was loud and snapping. No thrills were felt. The abdomen was obese but no organs, masses, tenderness, or ascites were found. The genitalia were normal. The right leg had been previously amputated above the knee. There was no edema of the left ankle, but marked pitting edema was present in the upper extremities. The neurological examination was negative.

Laboratory findings were as follows: The urinalysis was normal except for 0.25 per cent sugar being present. The red blood cell count was 4.06 million, the hemoglobin was 13 grams per 100 c.c., and the white blood cell count was 16,850, with 80 per cent polymorphonuclear neutrophiles. The orthodiagram showed marked widening of the mediastinum, especially to the right, with fluid being present in the left lung base (Fig. 1). No unusual aortic pulsations were noted. The electrocardiogram was normal except for lowered R waves in the chest leads.

The tentative diagnosis was obstruction of the superior vena cava probably due to mediastinal lymphoblastoma. Deep roentgen therapy was given to the mediastinal area. Some improvement of the dyspnea and edema was noted and the patient was discharged on Oct. 4, 1946. He was readmitted to the hospital on Oct. 25, 1946, in a moribund state. His dyspnea was marked and his eyelids were swollen shut, yet no edema of the lower extremities was present. He died a few hours later.

Necropsy.—The upper anterior mediastinum was found to be occupied by a large, infiltrating tumor mass. The wall of the superior vena cava had been invaded by tumor tissue and its lumen was occluded by a thrombus which extended into both innominate veins. The microscopic diagnosis of the tumor was Hodgkin's sarcoma.

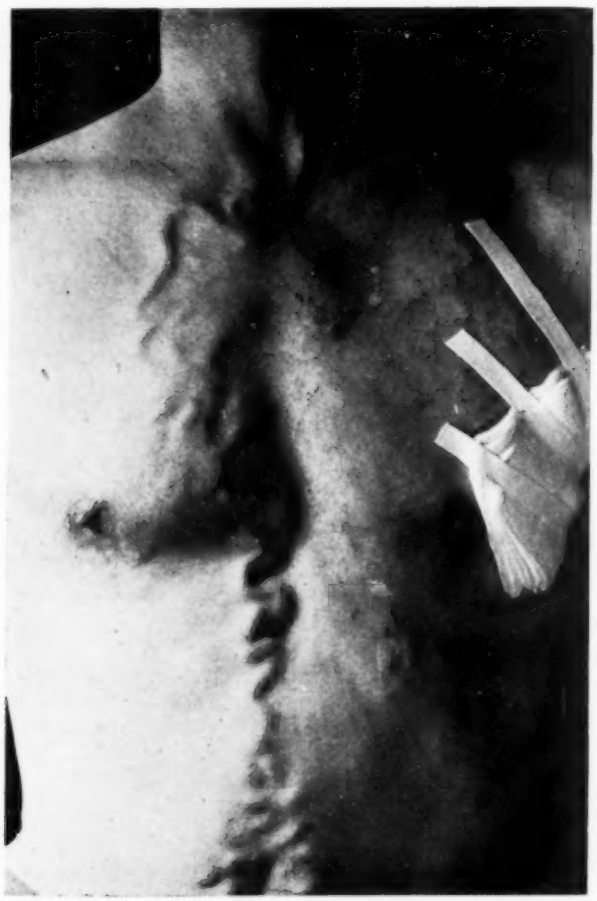


Fig. 2.—Case 2. Photograph of anterior chest wall showing dilated veins. Note the patch of dilated venules to the left of the upper sternum and over the left costal margin.

Comment.—This case is an example of the commonest form of thrombosis of the superior vena cava. As was the case in this instance, the thrombus is usually secondary to invasion of the vein wall by a malignant mediastinal neoplasm.

CASE 2.—The patient was a 45-year-old white man who entered the White Memorial Hospital on Nov. 4, 1946. He complained of "flushing and swelling" of the face, head, and neck, which had been present for two years. He had also noted dilated anterior chest veins for one and one-half years. Probably these symptoms had developed gradually, as the patient could give no exact date as to their onset. The sensation of flushing and fullness of the face and head was aggravated consistently by lying down or by stooping and by exercise. Edema of the eyelids and hands had been noted by the patient on arising in the morning. Tightness in the throat and slight dyspnea were noted upon exertion. No orthopnea, cough, wheezing, hoarseness, weight loss, or chest pain was ever experienced. Edema in the lower extremities was never noted. Fever had not been present at any time and enlarged lymph nodes were never found.

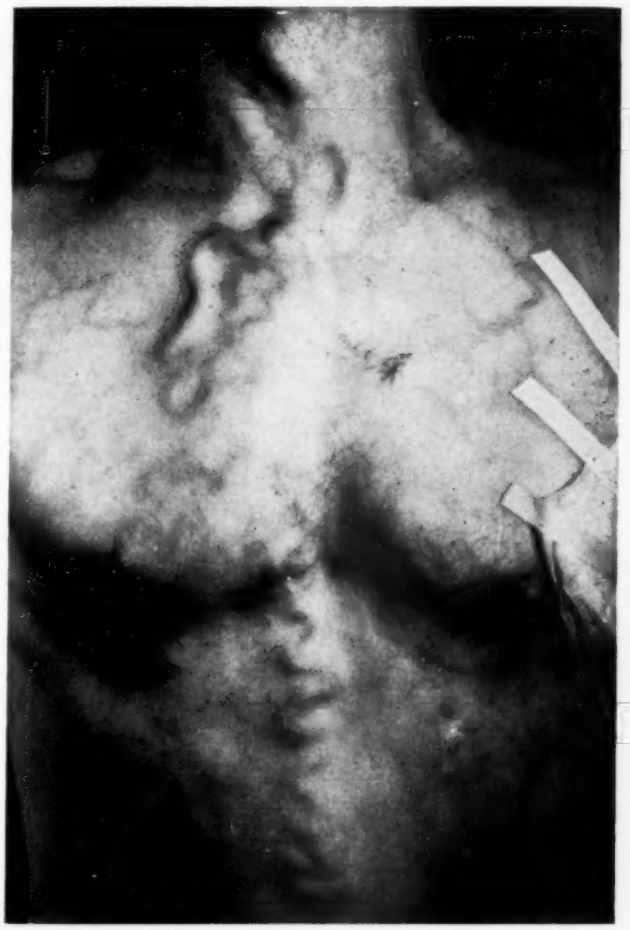


Fig. 3.—Case 2. Infrared photograph showing widespread dilatation of the veins of the anterior chest.

Past history did not reveal chest trauma, pulmonary tuberculosis, syphilis, or any other pulmonary, cardiac, or systemic illnesses. The patient had had gonorrheal urethritis twenty-four years previously.

Physical examination showed a well-developed, well-nourished white man in no acute distress, but anterior chest veins were markedly dilated and the face showed a dusky, flushed appearance. The blood pressure was 130/80 in both arms, the pulse was 84 per minute, the respiratory rate was 20 per minute, and the temperature was 98.6° Fahrenheit. The skin was clear except for a deep flushing of the face. The face and lips were slightly cyanotic. The ears, nose, throat, and eyes were not unusual and no evidence of Horner's syndrome was found. No particular engorgment of the neck veins was apparent, the thyroid gland was not palpable, and there was no cervical adenopathy. Large, tortuous veins covered most of the anterior chest wall. The largest of these veins extended downward over the abdomen and nearly to the pelvic brim (Figs. 2 and 3). These vessels filled from above at all levels. The heart was not enlarged. No murmurs were heard. Sinus rhythm was present. The lungs were clear throughout. A firm node, 1.0 cm. by 1.0 cm., was felt in the left axilla. The examination of the abdomen was normal except for the presence of large veins continuous with those on the anterior chest. No edema or deformities could be found in the lower extremities. The genitalia and the neurological examination were normal.

Laboratory Findings.— Laboratory findings revealed the following: Two urinalyses were normal and the Wassermann reaction was twice reported to be negative. The red blood count was 5.1 million and the hemoglobin was 16 grams per 100 c.c. of blood. The white blood count was 8,500 with a normal differential picture. The orthodiagram of the heart was not unusual. No mediastinal widening or abnormal pulsations were found. A sternal marrow study was reported as normal. A biopsy of the slightly enlarged left axillary lymph node revealed normal lymphoid tissue.

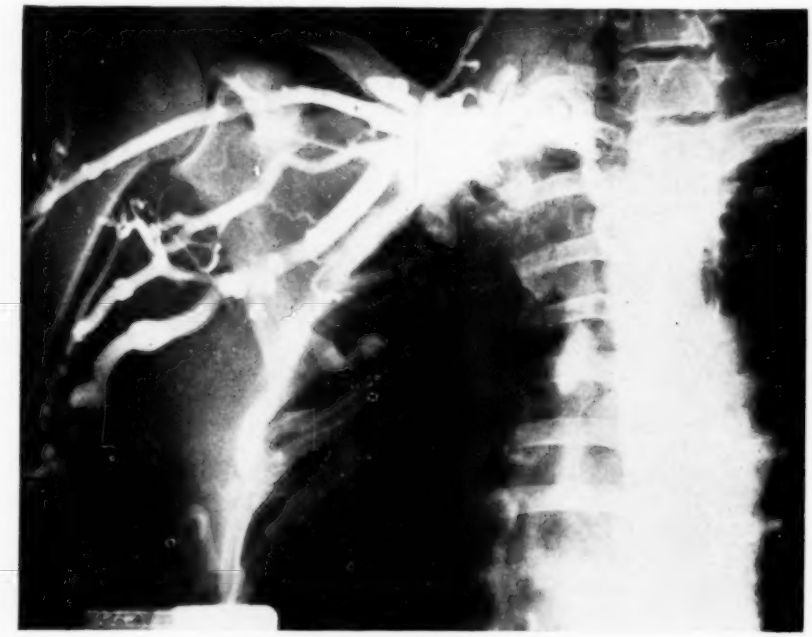


Fig. 4.—Case 2. Venograms showing dilated collateral veins of the anterior chest and evidence of venous obstruction in the region of both innominate veins. Left anterior oblique view of the right side.

Special Examinations.—In the right arm the venous pressure was 270 mm. of saline and the arm-to-tongue circulation time with magnesium sulfate was 25 seconds. In the left arm the venous pressure was 360 mm. of saline and the arm-to-tongue circulation time was 29 seconds. Normal venous pressure readings were found in the lower extremities. Venograms were made by the injection of 40 c.c. of 70 per cent Diodrast solution into the two respective antecubital veins as rapidly as possible through 16-gauge needles while serial roentgenograms were being taken. These venograms demonstrated almost complete obstruction of the superior vena cava and of the innominate veins as well (Fig. 4).

The patient has remained as he has been described for six months under observation. He carries on his work as a telegraph operator without difficulty and does not appear to be getting worse. In fact, many of his complaints are better. This improvement is probably due to improved collateral circulation.

Comment.—The history, the physical findings, the elevated venous pressures, and the definite evidence presented by the venograms are ample proof of the diagnosis of obstruction of the superior vena cava. To state the cause of the obstructing process with finality is difficult. All the evidence strongly suggests that the obstructing lesion is intraluminal. It is very probable that the causative factor was thrombotic in nature, and in view of the lack of evidence of any extraluminal lesion, one may suggest that a "primary" thrombosis of the superior vena cava is present. Several somewhat similar cases have been reported which ascribe the thrombus formation to "mediastinal fibrosis." However, in the majority of these cases some evidence of contributory mediastinal disease, such as syphilis or tuberculosis, was presented. No factors were found in this case which ordinarily are considered to promote thrombosis of the superior vena cava. Consequently, it is felt that this case may represent one of the rare primary cases of thrombosis of the superior vena cava.

SUMMARY AND CONCLUSIONS

1. The literature on obstruction of the superior vena cava has been reviewed and the 125 cases reported since 1934 have been collected and analyzed briefly.

2. Two additional cases, one of unusual interest, are reported in detail.

3. An outline of the important points in the diagnosis of the syndrome due to obstruction of the superior vena cava is presented.

4. Treatment, prognosis, and incidence have been discussed briefly.

The author wishes to thank Dr. John E. Peterson and Dr. Varner Jay Johns, Jr., for their kind permission to use the two cases presented in this paper.

REFERENCES

1. Ehrlich, William, Ballon, H. C., and Graham, E. A.: Superior Vena Caval Obstruction With Consideration of the Possible Relief of Symptoms by Mediastinal Decompression, J. Thoracic Surg. **3**:352, 1933.
2. Hussey, H. H.: The Effect of Mediastinal Lesions on Pressures in the Antecubital and Femoral Veins, AM. HEART J. **17**:57-68, 1939.
3. Pilcher, Lewis S., and Overholt, Richard H.: Venous Obstruction in the Upper Mediastinum, Ann. Surg. **100**:74-86, 1934.
4. Hinshaw, H. C., and Rutledge, D. I.: Lesions in the Superior Mediastinum Which Interfere With Venous Circulation, J. Lab. & Clin. Med. **27**:908, 1942.

5. Hussey, H. H., Katz, S., and Yater, W. N.: Superior Vena Caval Syndrome; Report of 35 Cases, AM. HEART J. 31:1, 1946.
6. Ramos, Jairo, Mercondes, J. Reynaldo, and Franchesi, Bernardino: Sindrome de Compressao da Veia Cava, Ann. paulist. de med. e. cir. 36:439-456, 1938.
7. Diefenbach, W. E., and Sunderg, R. H.: Obstruction of the Superior Vena Cava by Carcinoma of the Bronchus, California & West. Med. 41:40-42, 1934.
8. Fabris, A.: Neoplastic Thrombosis of the Superior Vena Cava Secondary to a Primary Tumor of the Lung, Policlinico (Sez. prat.) 42:607-613, 1935.
9. Mallory, T. B.: Obstruction of the Superior Vena Cava Due to Bronchogenic Carcinoma (A Clinicopathological Case), New England J. Med. 220:525-529, 1939.
10. Bosch, R. G.: Cancer Broncho-pulmonar; Sindrome Venoso Mediastinal Por Compresion de la Vena Cava Superior, Atelectasia Pulmonar. Día. Méd. 13:556-559, 1941.
11. Altschule, M. D., Aglaver, A., and Zamcheck, N.: Respiration and Circulation in Patients With Obstruction of the Superior Vena Cava, Arch. Int. Med. 75:24-29, 1945.
12. Holt, W. L., Jr.: The Extension of Malignant Tumors of the Thyroid Gland Into the Great Veins and Right Heart, J. A. M. A. 102:1921-1924, 1934.
13. Figoli, Carlos, and Menchaca, F. J.: Sindrome Mediastinal por Sarcoma Linfoblistico, Arch. argent. de pediat. 16:43-54, 1941.
14. Pujol y Izquierdo, Joaquin: La Disociacion de la Presion Venosa Periferica y de la Velocidad Circulatoria, signo Caracteristico de la Obstruccion de la Vena Cava Superior, Rev. cubana de cardiol. 2:25-32, 1939.
15. Martin, Réne, Martin, Rouesse, and Martin, Fioconni: Slow Compression of Superior Vena Cava by a Mediastinal Tumor, Bull. et. mém. Soc. méd. hôp. de Paris 50:192-198, 1934.
16. Flava, Pedro, and Fonseca, Aloysio: "Sindrome Mediastinica," Rev. méd. brasil. 867-878, 1940.
17. Armstrong, E. L., Coggin, C. B., and Hendrickson, H. S.: Spontaneous Arteriovenous Aneurysms of the Thorax, Arch. Int. Med. 63:298-317, 1939.
18. Schweiger, L. R., Burchell, H. B., and Baggenstoss, A. H.: Spontaneous Arteriovenous Communication Between the Aorta and Superior Vena Cava, Ann. Int. Med. 19: 1029-1034, 1943.
19. Barker, J. N., and Yater, W. N.: Arteriovenous Fistula Between the Ascending Aorta and the Superior Vena Cava, M. Ann. District of Columbia, 11:439, 1942.
20. Mebra, J. A., and de Oliveda, H. L.: Intrapericardiac Aneurysm of the Aorta With Rupture Into the Superior Vena Cava, Arg. de cir. clin. e exper. Num. Espec., p. 497, 1941.
21. Segadas, R.: Perforation of Aortic Aneurysm Into Superior Vena Cava, Rev. med.-cir. do Brasil 46:1044, 1938.
22. Meskauskas, J.: Aortic Aneurysm Perforated Into the Superior Vena Cava, Medicina, Kaunas 19:418, 1938.
23. Brunewitich, K.: Rupture of an Aortic Aneurysm Into the Superior Vena Cava, Zentralbl. f. inn. Med. 59:354, 1938.
24. Roch, M.: Cyanosis and Collar Edema Due to Perforation of a Syphilitic Aortic Aneurysm Into the Superior Vena Cava, Presse méd. 45:363, 1937.
25. Klinck, G. H., Jr.: Aneurysm of the Aorta With Rupture Into the Superior Vena Cava, Albany M. Ann. 55:125, 1936.
26. Marques, A.: Aneurisma Artiovenoso da base do Coracao, Rev. med. de Pernambuco. 5:183, 1935.
27. Graham, W. E., and Weisross, S.: Rupture of an Aortic Aneurysm Into the Superior Vena Cava, Mil. Surgeon 76:26, 1935.
28. Baker, L. A.: Dissecting Aneurysm of the Aorta With Complete Obstruction of the Superior Vena Cava, M. Bull. Vet. Admin. 17:170-174, 1940.
29. Zemon, F. D.: Occlusion of the Superior Vena Cava Due to Syphilitic Mediastinitis, J. Thoracic Surg. 14:330-338, 1945.
30. Forster, D. E.: Superior Vena Caval Obstruction, Clinics 1:591-599, 1942.
31. Gray, Howard K., and Skinner, Ira C.: Constrictive Occlusion of the Superior Vena Cava, Surg. Gynec. & Obst. 72:923-929, 1941.
32. Rutledge, D. I., and Gray, H. K.: Indeterminate type of Obstruction of the Superior Vena Cava, Proc. Staff Meet. Mayo Clin. 14:337, 1939.
33. Ergonian, Jane, and Wade, L. J.: Chronic Fibrous Mediastinitis With Obstruction of the Superior Vena Cava, J. Thoracic Surg. 12:275-284, 1943.
34. Ochsner, Alton, and Dixon, J. L.: Superior Vena Caval Thrombosis: Review of the Literature and Report of Cases of Traumatic and Infectious Origin, J. Thoracic Surg. 5:641-672, 1936.
35. Ragins, O. B., and Coe, G. C.: Superior and Inferior Venae Caval Thrombosis With Polycythemia: Report of Case, Ann. Int. Med. 19:496-501, 1943.
36. Blasingame, F. J. L.: Thrombotic Occlusion of the Superior Vena Cava and Its Tributaries, Associated With Established Collateral Circulation, Arch. Path. 25:361-364, 1938.
37. Soloff, L. A.: Syndrome of Superior Vena Caval Obstruction, AM. HEART J. 18:318-328, 1939.

38. Domenighine, Riccardo: Su un Casodi Ostruzioni Nel Territorio Della Cava Superiore ed Inferiore, Gazz. d. osp. **60**:535-544, 1939.
39. Burlando, A. J., and Oribe, H. R.: Thrombosis de la Vena Cava Superior, Radiología **5**:119-124, 1942.
40. Santiago, Dwight, and Stevenson, A.: Thrombosis of the Superior Vena Cava Following Osteomyelitis and Septicemia, Puerto Rico J. Pub. Health & Trop. Med. **18**:125, 1942.
41. Szour, Michel, and Berman, R.: Thrombosis of the Superior Vena Cava in Pulmonary Tuberculosis, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:192-198, 1934.
42. Master, A. M., and Russell, T. B.: Acute Coronary Artery Occlusion With Intraventricular Septal Perforation. Bernheim Syndrome and Superior Vena Caval Obstruction Diagnosed Clinically, Ann. Int. Med. **22**:440-447, 1945.
43. Kammer, Victor: Thrombosis of the Vena Cava Superior, East African M. J. **10**:317-320, 1943.
44. Brizzard, E. N.: Thrombosis of the Superior Vena Cava, Brit. J. Tuberc. **34**:39-44, 1940.
45. Cleland, W. P.: Thrombosis of the Superior Vena Cava and Pulmonary Veins, Brit. J. Tuberc. **35**:141-146, 1941.
46. Stuhlinger, H., and Bartsch, G. H.: Thrombosis of the Superior Vena Cava, Ztschr. f. Kreislaufforsch. **33**:401-414, 1941.
47. Poinso, R., and Carcassonne, F.: Syndrome Médiastinal et Localisations Anormales au Début d'une Leucémie Aiguë, Sang. **11**:62-66, 1937.
48. Blanco, Piazzio, Dighiero, Jorge, and Malosetti, H.: Sindrome de Compression de la Vena Cava Superior Por la Auricular Isquierda en la Estiechez Mitral, Arch. urug. de med., cir. y Especialid **21**:630-638, 1942.
49. Jeannin: Non-Tuberculous Pneumothorax Causing Superior Vena Caval Obstruction in a 2 Months Old Infant, Bull. Soc. de Pediat. de Paris **32**:289-292, 1934.
50. Carlson, H. A.: Obstruction of the Superior Vena Cava (Experimental Study), Arch. Surg. **29**:669-677, 1934.

CONGENITAL DEXTROCARDIA WITH SITUS INVERSUS COMPLICATED BY HYPERTENSIVE HEART DISEASE; REVERSAL OF HYPERTENSIVE CHANGES FOLLOWING THORACOLUMBAR SYMPATHECTOMY

JERALD S. KALTER, M.D.
NEW YORK, N. Y.

WHILE dextrocardia with or without situs inversus is not a rare condition, its incidence having been estimated by LeWald[1] to be one in 35,000 Army recruits and by Parson[2] to be two in approximately 15,000 private patients, the finding of dextrocardia in association with acquired organic heart disease is exceptionally rare. Manchester and White[3] reviewed reports on dextrocardia from the time of Aristotle and found that it is not rare. In the cases reported, the only ones similar to the case to be presented are those reported by Willius[4] in 1931 and the case reported by Manchester and White in 1938. However, as far as can be determined, this is the first case of dextrocardia complicated by hypertension and cardiovascular disease in which reversal of the electrocardiographic picture occurred as a result of a Smithwick thoracolumbar sympathectomy.

REPORT OF CASE

A. B., a 35-year-old chief petty officer in the United States Navy, was admitted to the hospital on May 6, 1946, because of headaches, dizziness, and hypertension. Aside from attacks of palpitation associated with very rapid pulse occurring sporadically over a period of ten years, he had been in excellent health and had performed the arduous duties of a chief petty officer in wartime. There had been no illness except for the usual childhood diseases. He had a tonsillectomy in 1942 and a broken right tarsal navicular bone in June, 1945. He smoked an occasional cigar, drank beer and coffee occasionally, and denied any venereal disease. He had been married five years and had no children. About three months prior to the time of hospital admission, the patient began to complain of frequent headaches, particularly on change from a supine to an upright position. The headaches had been associated with dizziness and a feeling of lightheadedness and lasted from a few hours to several days. Because of these complaints and the presence of hypertension, the patient was admitted to the hospital for evaluation.

The family history revealed that the father had died from hypertension and heart disease at the age of fifty-three; the mother was living and well; one brother had died as a result of drowning, and four sisters were living and well.

Physical Examination.—The patient was heavy set and gray haired, and appeared older than his stated age. His temperature was 98.6° Fahrenheit. His pulse was regular at the rate of 62 per minute and his respiratory rate was 18. Blood pressure was 180/130. He was 71 inches tall and weighed 210 pounds. The only significant finding in the examination of the head and neck

From the Heart Station at the U. S. Naval Hospital, St. Albans, N. Y.

The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

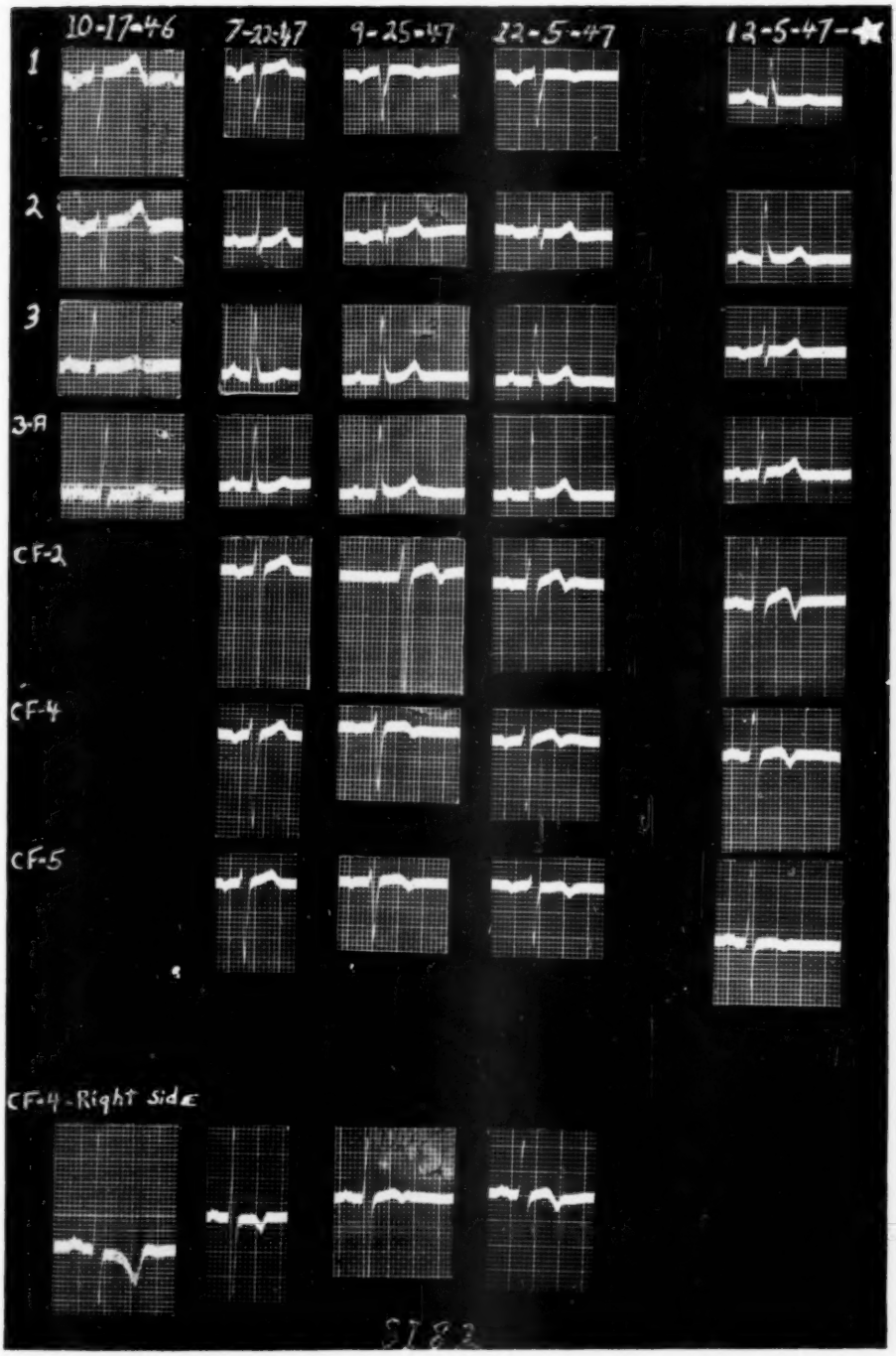


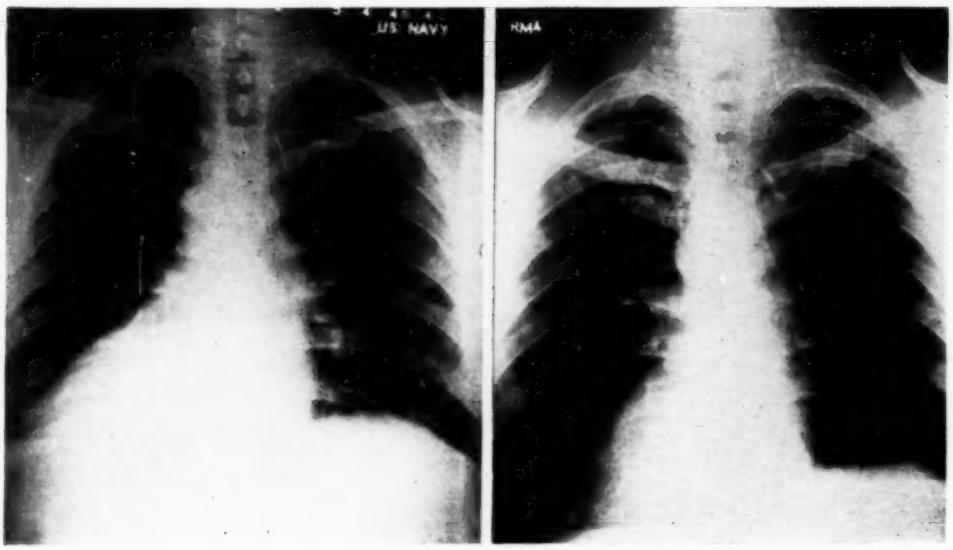
Fig. 1.—10/17/46: Original electrocardiogram showing the picture of dextrocardia complicated by "left" ventricular strain. 7/22/47: Twenty days after second stage sympathectomy: essentially no change. 9/25/47: Signs of "left" ventricular strain are disappearing. 12/5/47: Further improvement. 12/5/47*: Tracing taken with the limb leads reversed.

was that the ocular fundus adjacent to the disc showed slightly increased glial tissue with several instances of arteriovenous compression at the crossings. The ratio of the width of the arteries to the width of the veins was decreased with an irregularity in the caliber of the arteries and a widening of the light streak. The picture was that of early hypertensive retinopathy, Grade 1 to 2.

The apical impulse of the heart was palpable outside the midclavicular line 11.5 cm. to the right of the midsternal line in the right fifth intercostal space. The left border showed dullness 3.0 cm. to the left of the midsternal line in the fourth intercostal space. The second sound was louder in the left second intercostal space, which in this case corresponded to the second aortic sound, than in the right second intercostal space. There were no murmurs and no arrhythmias. The pulses were full, regular, and equal. There was no evidence of cardiac decompensation. The physical examination was otherwise negative.

Roentgenologic examination of the chest revealed transposition of the heart and slight cardiac enlargement to the right (Fig. 2, *A*). The aorta extended upward to the right and the aortic arch could be visualized in the right anterior oblique view. The left leaf of the diaphragm was higher than the right and diaphragmatic excursion was normal. Gastrointestinal examination demonstrated a transposition of the abdominal organs.

The electrocardiogram (Fig. 1) showed normal sinus rhythm, a ventricular rate of 60, marked right axis deviation, a P-R interval of 0.16 second duration, and a QRS complex of 0.08 second duration. The P waves and the QRS complexes in Leads I and II were inverted, while the T waves in all limb leads were upright. The T waves in Lead IV F, which was taken over the cardiac apex on the right side, were inverted.



A. *B.*

Fig. 2.—*A*, Teleroentgenogram taken 5/4/46. *B*, Teleroentgenogram taken 9/9/47.

Laboratory studies, including complete blood count, sedimentation rate, and Kahn, blood chemistry, urinalysis, and renal function tests, were all within normal limits. Blood pressure remained persistently elevated between 154/118 and 190/144.

The sodium amytal test lowered the blood pressure to 120/90 within three hours. A cold pressor test caused a rise in blood pressure from 156/120 to 198/180 within thirty seconds and a return to 166/140 within ten minutes.

At first the patient was placed on conservative management, including sedation and a reducing diet, in order to evaluate his symptoms. On Feb. 6, 1947, a left thoracolumbar sympathectomy from the eighth thoracic to the third lumbar ganglion was performed. The patient

withstood the procedure well, but his postoperative course was complicated by a pleural effusion and pneumothorax which required repeated aspirations. He was given time to recuperate sufficiently and on July 2, 1947, a right thoracolumbar sympathectomy from the fourth thoracic to the second lumbar ganglion was performed.

The patient recovered from this procedure rapidly except for an attack of auricular tachycardia which persisted for five days and was eventually controlled by quinidine. Blood pressure readings ranged from 108 to 120, systolic, and from 60 to 80, diastolic, for the first few weeks. The patient noted some hypotensive weakness and was provided with an abdominal belt. On Dec. 5, 1947, the patient was seen again and at this time he was completely asymptomatic, having been entirely free of any episode of palpitation and tachycardia for the first time in ten years. His blood pressure was 125/88. The eye grounds revealed a slight narrowing of the arteries with two instances of slight arteriovenous compression. The right border of cardiac dullness was 10.0 cm. to the right of the midsternal line and the remainder of the physical findings were essentially unchanged.

Postoperative electrocardiographic examination showed a normal sinus rhythm. The P-R interval was 0.17 second, while the duration of the QRS complex was 0.10 second. The P waves and the QRS complexes in Lead I were inverted, and there was marked right axis deviation. However, the T waves in Lead I, previously upright, had now become inverted.

DISCUSSION

Despite the fact that he had been examined physically on numerous occasions during the previous ten years because of episodes of palpitation and tachycardia, this patient had never been discovered to have dextrocardia until admission to the hospital, where this was confirmed by electrocardiographic and x-ray studies. The interesting feature of the electrocardiogram was that the T wave in Lead I was upright and the T wave in Lead IV F, taken over the cardiac apex on the right side, was inverted, indicating that this was the picture of "left" ventricular strain superimposed upon that of dextrocardia. In view of the fact that this was rapidly progressing, having appeared since the patient's last annual physical examination and because it was associated with symptoms and early eye-ground and electrocardiographic changes, the patient was placed upon a regime of sedation and weight reduction in an attempt to improve his condition.

However, after a period of nine months and a twenty-pound weight loss, there was essentially little change in his condition and, therefore, a left thoracolumbar sympathectomy was performed. Five months later a right thoracolumbar sympathectomy was performed, which, because of the patient's history of frequent episodes of tachycardia, was carried up to the fourth thoracic ganglion.

The patient's blood pressure returned to normal and has remained within normal limits. His symptoms completely disappeared and have not returned. The heart size has become smaller, as shown in Fig. 2, *B*, and the presence of "left" heart strain in the electrocardiogram has largely disappeared. As will be seen in Fig. 1, the evidence of heart strain was still present on July 23, 1947, approximately three weeks after the second operation, but on Sept. 25, 1947, was beginning to disappear. Confirmatory evidence of the disappearance of electrocardiographic signs of heart strain is shown in the tracing of Fig. 1* which was taken with the arm wires reversed, thus correcting for the dextrocardia.

SUMMARY

A case of congenital dextrocardia with situs inversus complicated by cardiovascular disease is presented. The interesting features are that the symptomatic, roentgenographic, and electrocardiographic findings due to hypertension were reversed by a Smithwick thoracolumbar sympathectomy, leaving the patient with his original congenital anomaly. There is no record of any other similar case, but presumably, if sympathectomies in hypertensive disease become more frequent, other such cases will be encountered.

REFERENCES

1. LeWald, L. T.: Complete Transposition of the Viscera; A Report of Twenty-nine Cases, With Remarks on Etiology, J. A. M. A. **84**:261, 1925.
2. Parson, G. W.: Dextrocardia With Situs Inversus Complicated by Chronic Rheumatic Aortic and Mitral Endocarditis, Ann. Int. Med. **23**:102, 1945.
3. Manchester, B., and White, P. D.: Dextrocardia With Situs Inversus Complicated by Hypertensive and Coronary Heart Disease, AM. HEART J. **15**:493, 1938.
4. Willius, F. A.: Congenital Dextrocardia With Situs Transversus Complicated by Hypertensive Heart Disease; Electrocardiographic Changes, AM. HEART J. **7**:110, 1931.
5. Crawford, J. H., and Warren, C. F.: Coronary Thrombosis in a Case of Congenital Dextrocardia With Situs Inversus, AM. HEART J. **15**:240, 1938.
6. Stubenbord, W. D.: Dextrocardia in Association With a Short P-R Interval With Prolongation of the QRS Complex, U. S. Nav. M. Bull. **46**:412, 1946.

CONGENITAL ANEURYSM OF THE RIGHT ANTERIOR SINUS OF VALSALVA (INTERVENTRICULAR ANEURYSM) WITH SPONTANEOUS RUPTURE INTO THE LEFT VENTRICLE

ROBERT ORR WARTHEN, M.D.
WASHINGTON, D. C.

SPONTANEOUS rupture into the left ventricle of a congenital aneurysm of the right anterior sinus of Valsalva of the aortic valve is an occurrence heretofore undescribed in the literature. Such a case is herewith presented along with a brief discussion of the condition and of the interesting clinical aspects involved.

CASE REPORT

A. S., a 38-year-old Negro mechanic, was first admitted to Gallinger Hospital on Dec. 2, 1946, with the complaints of swollen feet of three days' duration and cough of two months' duration. He had apparently been perfectly well until the development of a "hacking cough," which was productive of a white, foamy sputum two months prior to admission. This persisted, and one and one-half months before admission, he began experiencing mild dyspnea on exertion which soon became severe and progressed to orthopnea. One month before admission, while working, he experienced a sudden dull midsubsternal pain which radiated to both the right and left upper abdominal quadrants. This pain persisted for several hours and was aggravated by numerous coughing spells. Two and one-half weeks later he began experiencing nausea and vomiting following his coughing spells. A progressive swelling of his feet occurred during the three days prior to his admission.

At the age of 24 years a vague attack of "rheumatism" had occurred. He had had an untreated "penile sore" lasting for two weeks at the age of 28 years. No serologic test for syphilis was performed at that time. During the two years prior to his hospitalization he had been hoarse as a result of undetermined reasons.

Physical examination on admission revealed a chronically ill and orthopneic Negro man, who appeared to be his stated age. The blood pressure was 180/40 to 20; the pulse was 100 per minute and of the waterhammer type; respirations were 24 per minute; and the temperature was 98.6° Fahrenheit. The anterior cervical and inguinal lymph nodes were palpable and small. The neck veins were slightly engorged and pulsating. The respirations were rapid and shallow. Crepitant râles were heard over both lungs. The heart was enlarged. Its left outermost border was 14 cm. from the midsternal line in the sixth anterior intercostal space. The point of maximal impulse was in the fifth left intercostal space at the anterior axillary line. A blowing aortic diastolic murmur was transmitted along the left sternal border to the apex and to the left axilla. A localized, soft, aortic systolic murmur was also described, as were a harsh apical diastolic murmur and a long, soft, apical systolic murmur. The rhythm was regular. The abdomen was moderately distended with bulging in the flanks. There was a questionable fluid wave and a palpable, tender liver which extended downward to the level of the umbilicus. There was 1 to 2 plus pitting edema of the legs, ankles, feet, and sacrum. The remainder of the physical examination, including the neurological, was essentially negative.

From the Department of Pathology, George Washington University School of Medicine, Washington, D. C.

Laboratory examinations revealed a negative blood Kahn test on two occasions and a urea nitrogen of 10 mg. per cent. An electrocardiogram showed left axis deviation, right bundle branch block, and a questionable, associated first degree A-V block. An x-ray film of the chest disclosed moderate pulmonary congestion and enlargement of the heart downward and to the left with a normally outlined aorta. The transverse diameter of the heart was 19 cm., while that of the chest was 32 centimeters.

The patient's congestive heart failure was controlled by the tenth hospital day after he had received digitalis, Mercupurin, and ammonium chloride therapy. Because of a persistent hoarseness a laryngoscopic examination was performed on the fifteenth day and chronic laryngitis was diagnosed. Nineteen days after admission he was released against the advice of the staff.

On Jan. 10, 1947, he again returned to the hospital with complaints similar to those on the previous admission. Physical examination at that time revealed a blood pressure of 160/40 and edema of the legs, ankles, and feet of greater severity than previously. Abdominal shifting dullness without a fluid wave was present. The remainder of the physical examination was essentially the same as that of the previous admission. Treatment consisted of digitalization and diuresis with Mercupurin and Aminophyllin. A venous pressure of 310 mm. H_2O was obtained on admission. An x-ray film of the chest disclosed a picture similar to that on the first admission. A repeat blood Kahn test was negative and the blood urea nitrogen was 13 mg. per cent. He was discharged on Feb. 7, 1947, to be followed in the cardiac clinic.

The final admission was one month later on March 7 when he again presented a history similar to that of the two preceding admissions. For a week prior to that admission he had failed to take diuretics and digitalis as prescribed. The blood pressure was 165/50, the pulse was 96 per minute, the respirations were 24 per minute and the temperature was 99° Fahrenheit. The lungs revealed fine inspiratory râles at the left base and an absence of breath sounds at the right base. The heart was enlarged as described on previous admissions. A loud mid-diastolic murmur with its maximum intensity in the fourth left intercostal space at the sternal border was transmitted downward to the apex. A systolic apical murmur which was transmitted to the left axilla and angle of the left scapula was also described. The remainder of the physical examination was essentially unchanged from the previous admissions. A venous pressure of 350 mm. H_2O rising to 450 mm. on right upper quadrant pressure was obtained on admission. A blood Kahn test was negative.

Several mild bouts of hemoptysis occurred four days after admission. An x-ray film of the chest at that time showed congestion with fluid at the right base and a density over the left costophrenic angle which was interpreted as a possible pulmonary infarct. A phlebothrombosis or thrombophlebitis of the upper or lower extremities was considered unlikely at that time. However, on the following day, because of bilateral calf tenderness and another bout of hemoptysis, a bilateral femoral vein ligation was performed. During the next two days several more bouts of hemoptysis occurred and the râles persisted at the left base. On March 16 he developed a moderately severe substernal and epigastric pain which was accompanied by a systolic blood pressure of 120, a pulse of 110 per minute, and roughened breath sounds and wheezes over both lung bases. Moderate upper abdominal tenderness was elicited.

He expired on March 17 after having experienced a rapid downhill course following his bout of substernal and epigastric pain.

Clinical Diagnosis.—(1) syphilitic aortitis with aortic regurgitation; (2) possible rheumatic heart disease; (3) congestive heart failure; and (4) pulmonary infarction.

Necropsy Report.—The pericardium revealed no abnormality; there were no pericardial adhesions, and 80 c.c. of clear, straw-colored fluid was present in the pericardial sac. The heart weighed 775 grams. It was greatly enlarged, firm in consistency, and was covered with a moderate amount of epicardial fat. On section, all chambers of the heart were found to be greatly dilated and there were no thrombi or emboli present. The tricuspid valve measured 16 cm. in circumference. Its cusps were moderately edematous at the tips and contained thin atherosclerotic plaques at the bases. The right ventricular wall measured 7.0 mm. in thickness and the papillary muscles were markedly hypertrophied. The chordae tendinae were not unusual and the pectinate

muscles were flattened. The pulmonary valve was dilated and measured 8.2 cm. in circumference. Several transverse fenestrations which were 5.0 mm. in length were present at the free edge of each cusp. The mitral valve was greatly dilated. It measured 15 cm. in circumference and its cusps were moderately thickened along the line of closure. The left ventricular wall measured 16 mm. in thickness and the papillary muscles were markedly hypertrophied. The chordae tendinae were slightly shortened, fused, and thickened; the pectinate muscles were flattened. The aortic valve measured 7.5 cm. in circumference at the ring. A transverse fenestration which was 3.0 mm. in length was present on the posterior cusp. It extended from the border of the left commissure onto the cusp and was parallel to and 1.0 mm. from the free edge of the cusp. The

Fig. 1.—Open left ventricle and aortic valve showing the large, gaping perforation of the right anterior sinus of Valsalva aneurysm.

right anterior cusp was slightly thickened along its free edge and was the seat of an aneurysm of the sinus of Valsalva. The aneurysm was a downward extension of the right anterior sinus of Valsalva into and dissecting the membranous portion of the interventricular septum. This aneurysm or sinus extended downward for a distance of 4.0 cm. below the level of the most inferior portion of the posterior and left anterior cusps to the trabeculated portion of the interventricular septum and measured 6.0 cm. in width. It produced its greatest bulge into the cavity of the left ventricle and lesser bulges into the cavities of the right auricle and right ventricle. A gaping perforation which measured 4.0 cm. in length was present on the left ventricular aspect

of the aneurysmal bulge and was located with its upper end at a point 6.0 cm. below the corpus arantii of the right anterior cusp, with its lower end 2.5 cm. inferior and to the right of the cusp. The inferior edge of this perforation was jagged, rough, and thickened and the superior edge was smooth. Figs. 1 and 2 show the opened left ventricle and aortic valve with the large, gaping perforation of the aneurysm of the right anterior sinus of Valsalva. The left anterior cusp was not unusual. The commissures of the cusp were not widened. The cusps were not rolled or shortened and their edges were free of abnormalities. The coronary ostia were patent, as were the coronary vessels throughout. A few yellowish-white, atherosclerotic subintimal plaques were noted in the descending thoracic and abdominal aorta. There was no gross evidence of syphilitic aortitis.

Fig. 2.—Opened left ventricle and aortic valve showing the large, gaping perforation of the right anterior sinus of Valsalva aneurysm.

Examination of the lungs revealed dense parietovisceral pleural adhesions in the right apex, left apex, left upper lobe laterally and posteriorly, and left lower lobe anteriorly, posteriorly, and laterally. These were associated with bilateral clear, straw-colored pleural effusions. The right pleural space contained 1,500 c.c. of fluid and there was 150 c.c. in the left pleural space.

The right lung weighed 1,100 grams and the left weighed 1,200 grams. Both showed marked congestion and edema. In addition, there was a thrombus in the medium-sized pulmonary artery which supplied the lower one-fifth of the left upper lobe. Distal to and surrounding this thrombosed vessel was a deeply hemorrhagic, firm triangular area. The thrombosed vessel represented its apex and the lung periphery, its base. The base of this triangular area measured 9.0 cm. in diameter and was on the anterolateral and inferior surfaces of the lobe. It extended 6.0 cm. distal to the apex. The bronchi were moderately congested and were filled with abundant frothy, blood-tinged fluid.

The liver was markedly enlarged and presented a "nutmeg" appearance; the spleen was somewhat atrophic.

The femoral veins were explored both proximal and distal to their ligated points. No abnormality was noted in the left; however, a thrombus was present in the right femoral vein proximal to the ligature. The proximal portion of the thrombus was attached to the intima at the point of the ligature and its distal end was free in the lumen of the vessel.

The remainder of the gross examination revealed no abnormality.

Anatomical Diagnosis.—(1) Congenital aneurysm of the right anterior sinus of Valsalva of the aorta, extending within the vestibular portion of the interventricular septum, with perforation of the left ventricular wall of the aneurysm; (2) aortic valve insufficiency; (3) congenital fenestrations of the pulmonic and aortic cusps; (4) hemorrhagic infarct of the left upper lobe with thrombosis of a pulmonary artery; (5) pulmonary hyperemia and edema, severe; (6) cor bovinum; (7) hydrothorax, bilateral; (8) thrombosis of the right femoral vein; and (9) pleural adhesions, bilateral.

Microscopic Examination.—The gross and microscopic findings agreed essentially. Sections of the myocardium revealed a moderate degree of replacement fibrosis and marked muscle hypertrophy. The mitral valve was moderately thickened by hyaline and fibrous connective tissue. There was no evidence of rheumatic valvulitis. The anterior mitral papillary muscle contained a small amount of interstitial fibrous connective tissue. Numerous sections through the walls of the aneurysm revealed dense hyaline and fibrous connective tissue. The borders of the perforation were lined by endocardium and were composed of a dense fibrous and hyaline connective tissue stroma. However, this tissue was interspersed with rare small and large round cells and polymorphonuclear leucocytes. Vascular elements were scarce. A thin layer of endocardium lined all sections of the aneurysm.

The ascending and transverse aorta showed no microscopic evidence of syphilis or arteriosclerosis. There was no evidence of ulcerative endocarditis or mycotic infection.

A minimal amount of coronary atherosclerosis without appreciable narrowing of the coronary lumina was noted.

DISCUSSION

Aneurysms or aneurysmal dilatations may originate in one or more of the sinuses of Valsalva of the aortic valve.[1] These aneurysms are inferior extensions or excavations of the sinuses and their walls depend on the sinus or sinuses involved.

Of most frequent occurrence is an aneurysm of the right anterior sinus,[2,3] which is also called an interventricular aneurysm and which extends downward as it dissects the membranous, nontrabeculated aortic vestibule and interventricular septum. It does not involve the muscular or trabeculated portion of the interventricular septum. The cavity so produced is related to the left ventricle on one side and to the right auricle and right ventricle on the other. It produces bulgings of the corresponding walls of those chambers.

Even rarer are aneurysms of the left anterior and the posterior sinuses of Valsalva. The left anterior sinus is the only one related to the external surface

of the heart and, when dilated, produces a bulging into the pericardial sac to the left of the pulmonary artery. This also extends into the membranous, nontrabeculated aortic vestibular wall down to the muscular or trabeculated ventricular wall and internally is related to the cavity of the left ventricle. An aneurysm of the posterior sinus (noncoronary sinus) of Valsalva also extends downward in the wall of the aortic vestibule and bulges anteriorly into the left ventricle and posteriorly into the right and left auricles.

These aneurysms of the sinuses of Valsalva have been ascribed to syphilis, arteriosclerosis, mycotic infections, ulcerative endocarditis, and congenital lesions.[3,4,5]

Depending on the anatomic location of the aneurysmal bulge, a number of complications may ensue. These aneurysms frequently rupture although death may or may not occur immediately. The perforation may occur in the right atrium, right ventricle, left atrium, left ventricle, pericardial sac, mediastinum, pulmonary artery, superior vena cava, and left pleural cavity.[3,4,6,7] A rare case in which the pericardial sac was obliterated and the aneurysm eroded through the chest wall to rupture externally has been recorded.[4] The most frequent clinical picture of aneurysm of one or more of Valsalva's sinuses is that of aortic insufficiency or regurgitation,[3,8] due to dilatation of the aortic ring. Bulging of the aneurysm into the right ventricle may produce a clinical picture of stenosis or insufficiency of the tricuspid valve and/or pulmonary stenosis.[1] Encroachment of an aneurysm of the right anterior sinus on the A-V node or bundle of His in the interventricular septum often leads to heart block or other A-V conduction defects.[1,4,5,6] Rare cases of myocardial infarction caused by the compression of a coronary artery by an extrinsic aneurysm of the sinus of Valsalva have been reported.[4,9]

Death is usually the result of one or more of the mentioned complications and congestive heart failure.

The case reported here represents one of an aneurysm of the right anterior sinus of Valsalva of the aortic valve which bulged into the left ventricle and to a lesser degree into the right auricle and right ventricle and which ruptured into the left ventricular cavity. A congenital aneurysm with spontaneous rupture is postulated, as no pathologic evidence of syphilis, arteriosclerosis, mycosis, or ulcerative endocarditis was found. The spontaneous rupture of a similar congenital aneurysm into the cavity of the left ventricle has not to my knowledge been described heretofore in the literature. In retrospect, after having examined the rupture point of the aneurysm both grossly and microscopically and having reviewed the patient's clinical history, it seems probable that the perforation occurred some months before death, perhaps just prior to the patients' first hospitalization.

During his first two hospital admissions his congestive failure was fairly well regulated by digitalis and diuretics. However, on his final admission, control was unsuccessful, probably because of the associated femoral vein thrombosis and pulmonary infarction. His death was no doubt the result of congestive heart failure with superimposed pulmonary infarction.

Clinically, he presented a typical picture of aortic insufficiency; hence, the erroneous diagnosis of syphilitic aortitis was made. This is readily understandable because aortic insufficiency is the most frequent clinical finding in patients with aneurysms of one or more of the sinuses of Valsalva.[4] The murmurs heard in the region of the mitral valve were probably due to dilatation of the valve ring, as a result of congestive heart failure. No microscopic evidence of rheumatic valvulitis was found.

The electrocardiographic findings that were observed (bundle branch block and questionable A-V block) are frequently found in cases of aneurysms of the sinus of Valsalva involving the interventricular septum because of encroachment of the aneurysm on the A-V node or the bundle of His.[10]

SUMMARY

1. The clinical and post-mortem findings of a case of congenital aneurysm of the right anterior sinus of Valsalva with spontaneous rupture into the left ventricle are presented and discussed.

2. This is believed to be the first published report of such a case.

REFERENCES

1. Micks, R. H.: Congenital Aneurysms of All Three Sinuses of Valsalva, Brit. Heart J. **2**:63, 1940.
2. Abbott, M. E.: Report of Cases, Brit. M. J. **2**:1197, 1932.
3. Herson, R. N., and Symons, M.: Ruptured Congenital Aneurysm of the Posterior Sinus of Valsalva, Brit. Heart J. **8**:125, 1946.
4. Chipps, H. D.: Aneurysm of the Sinus of Valsalva Causing Coronary Occlusion, Arch. Path. **31**:627, 1941.
5. Hirschboeck, F. J.: Aneurysm of One of the Sinuses of Valsalva Caused by a Congenital Lesion, Am. Heart J. **24**:550, 1942.
6. Duras, F. P.: Heart Block With Aneurysm of the Aortic Sinus, Brit. Heart J. **6**:61, 1944.
7. Kawasaki, I. A., and Benenson, A. S.: Rupture of an Aneurysm of a Sinus of Valsalva Into the Right Auricle, Ann. Int. Med. **25**:150, 1946.
8. Taussig, H. B., and Semans, J. H.: Severe Aortic Insufficiency in Association With a Congenital Malformation of the Heart of the Eisenmenger Type, Bull. Johns Hopkins Hosp. **66**:156, 1940.
9. Shuster, N. H.: Aneurysm of the Sinus of Valsalva Involving the Coronary Orifice, Lancet **1**:507, 1937.
10. Cossio, P.: Electrocardiograms in the Diagnosis of Certain Aneurysms of Valsalva's Sinuses (Intrapericardiac Aneurysms), Semana med. **41**:932, 1934.

ACUTE RHEUMATIC FEVER IN THE AGED

DAVID H. APPELMAN, M.D., MORRIS S. FEIMAN, M.D, AND LOUIS HARRIS, M.D.
BROOKLYN, N. Y.

THE acute rheumatic state is rare in the aged,[1,2,3,4] and rarer yet is an initial attack of acute rheumatic fever in the latter decades of life. It is the purpose of this communication to record a case in which an initial attack of acute rheumatic fever developed at 65 years of age. Rothschild, Kugel, and Gross[5] found only two cases of active rheumatic heart disease after the age of 50 and only one case after 60 years, but these were not initial attacks. In their study of 1,633 cases of rheumatic heart disease, DeGraff and Lingg[6] encountered only one patient who developed an initial infection past the age of 60. Rakov and Taylor[7] reported a case of rheumatic fever in a 61-year-old woman but stated in their summary that her initial rheumatic infection probably occurred in her childhood. Greene and Bennett[8] described a patient with an initial attack of rheumatic heart disease occurring at 64 years.

CASE REPORT

M. G., a white married woman, 65 years of age, had always been well and had done vigorous physical activity. She could not recall having had any symptoms of the rheumatic state, nor had any cardiac lesion ever been discovered. Except for a hysterectomy when she was 49 years old and four normal, full-term deliveries, she had required no medical attention. Questioning did not elicit any precipitating cause or the presence of any systemic disease prior to the onset of the present illness, which began three weeks before admission to the Beth-El Hospital on May 28, 1947. She had been well up to May 7, 1947, when she developed joint pains. The joint involvement was simultaneous, with the wrists, shoulders, knees, and ankles being particularly affected. There was pain, swelling, heat, and redness in the involved joints, and fever developed during the third week.

The patient presented the picture of an acute infection with hot, dry skin, anxious expression, and moderate prostration. The temperature was 103.4°F., the pulse rate was 98, and the blood pressure was 138/68. The wrists, shoulders, ankles, and knees were swollen, red, warm, and painful. There was limitation of motion of all joints. The skin was clear. The heart was not enlarged to percussion, and no murmurs or arrhythmias could be heard. The lungs were clear. The liver extended 2.0 cm. below the right costal margin but was not tender, and no pulsation could be felt. The spleen was not palpable. There was no edema of the lower extremities, except for the swelling of the ankles and knees. There were no other significant physical signs.

Laboratory examinations on the morning following admission revealed 11.0 Gm. of hemoglobin (71 per cent); a red blood cell count of 3,480,000; and a white blood count of 11,500. The differential count showed 78 per cent segmented neutrophiles, 15 per cent lymphocytes, and 7 per cent monocytes. The sedimentation rate was 18 mm. in seven minutes (Cutler method). Urinalysis was negative. An x-ray film of the chest on May 29 was read as follows: "The heart is of the

From the Department of Medicine, Beth-El Hospital, Brooklyn, N. Y.

aortic type and of normal proportional dimensions. The aorta, however, is elongated and widened, especially in the descending arcus. There is a calcific plaque in the arch. Hypertrophic osteoarthritic changes are noted in the dorsal spine." Roentgenologic studies of both hands showed hypertrophic osteoarthritis bilaterally. On May 31, the blood culture showed no organisms after forty-eight hours and an electrocardiogram revealed a P-R interval of 0.30 second.

Blood chemical examinations showed a serum protein of 6.6 Gm. per cent, with albumin of 3.7 Gm. per cent and globulin of 2.9 Gm. per cent. The blood urea nitrogen and sugar were within normal limits, and the uric acid was 1.5 mg. per cent. A Kline test was negative. Agglutination tests for brucellosis, typhoid, paratyphoid A and B, and typhus fever all were negative. Culture of a tonsillar swab revealed *Micrococcus catarrhalis* predominating with some pneumococci and staphylococci also present. The antifibrinolysin titer was 3 plus on June 10, and the same value was noted on June 18.

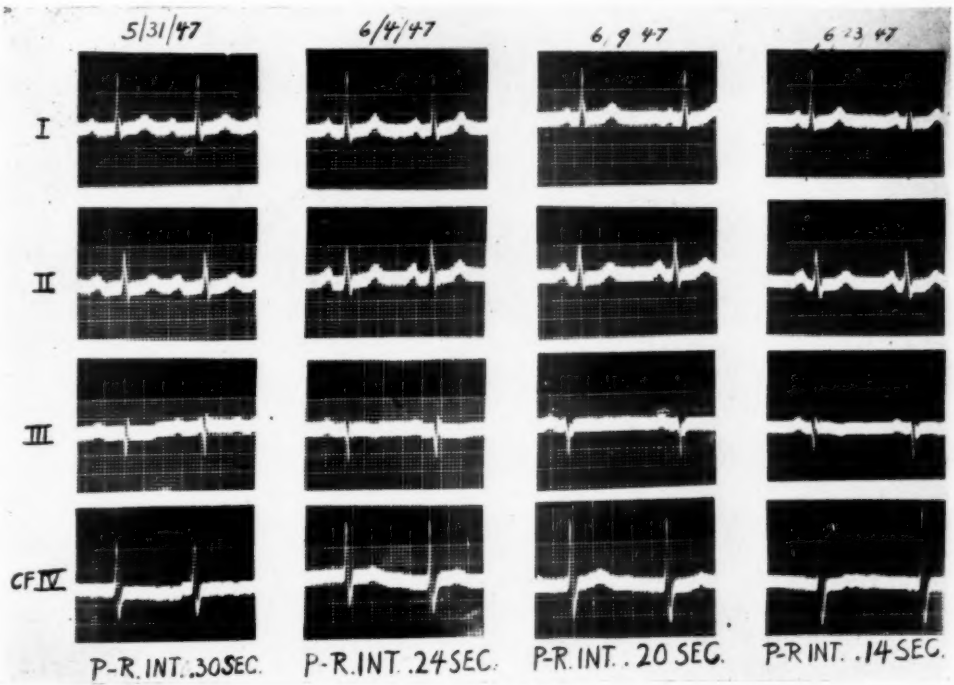


Fig. 1.—Serial electrocardiograms made during the acute illness.

Clinical Course.—The patient was confined to bed for six weeks. She received 20 grains of sodium salicylate and an equal amount of sodium bicarbonate four times daily from May 30 to June 29. From July 1 to the date of her discharge on July 16, she was given 15 grains of sodium salicylate three times daily, a 5.0 mg. tablet of vitamin K daily, a 250 mg. tablet of vitamin C each day, and two Feosol (three grains of ferrous sulfate) tablets three times daily. The fever, which had ranged between 100°F. and 103°F. for a week prior to admission, reached 102.6°F. on the first hospital day and gradually subsided to normal on the sixth day. Except for a temperature of 100.6°F. on the tenth day, she remained afebrile thereafter. The joint manifestations began to subside on the eighth day, with the swelling and warmth being alleviated first, while the pain on motion persisted until the second week. The joint symptoms completely subsided by the end of the third week. The pulse was 88 per minute on admission and ranged between 80 and 96 per minute during the first two weeks. Thereafter it fluctuated between 66 and 84 and never became irregular. No heart murmur was heard on admission. The con-

sulting cardiologist examined the patient on the eighth day and reported a faint systolic murmur at the apex. In the third week, a soft blowing diastolic murmur was heard along the left sternal margin in the fourth intercostal space, and persisted for four days. No murmur could be elicited thereafter.

An electrocardiogram taken on May 30 showed a P-R interval prolonged to 0.30 second. Subsequent electrocardiograms revealed the P-R interval to be 0.24 second on June 4, 0.20 second on June 10, and 0.14 second on June 23 (Fig. 1).

The sedimentation rate, which was 18 mm. in seven minutes (Cutler method) on the second day, was 18 mm. in twenty minutes on the eighth day, 18 mm. in forty minutes on the fifteenth day, and finally became 18 mm. in sixty-five minutes on the forty-second day. The leucocyte count was 11,500 on admission, declined to 7,750 on the eighth day, and remained from 5,000 to 6,000 after the third week. At the end of five weeks of treatment, the erythrocytes numbered 3,000,000 and the hemoglobin was estimated at 65 per cent. All urine examinations were negative. The blood salicylate level was 120 μg. per 100 c.c. on the seventh day, 380 μg. per 100 c.c. at the end of three weeks, and 168 μg. at the end of the fifth week.

At the time of discharge, there were no joint symptoms or complaints, and the temperature, P-R interval, sedimentation rate, and leucocyte count were all normal. There was, however, a persistent 3 plus antifibrinolysin titer.

COMMENT

It was apparent that the patient had suffered an initial attack of acute rheumatic fever despite her advanced age. Her previous history was negative for any previous attack of rheumatism, heart disease, or any joint pain; nor was there any antecedent history or positive evidence of the persistence of any specific infection.

Rheumatoid arthritis or chronic secondary infectious arthritis sometimes begins with the features of acute rheumatic fever. The initial and persistent involvement of small joints of the hands, feet, and spine and the comparative freedom from cardiac complications are suggestive features; and the persistence of periarticular swelling leading to obvious deformity confirms the diagnosis. However, none of these features was present in the case herewith reported.

Antitoxic or antibacterial serum therapy is often followed by serum sickness with polyarthritis as the chief symptom, but this patient had no coexistent urticaria and no history of serum treatment. She had received no penicillin treatment, which may occasionally cause a polyarthritis. There was no history of digitalis medication which might have caused the prolonged P-R interval. The persistently high elevation of the antifibrinolysin titer, although not specifically diagnostic, is a further link in the establishment of a diagnosis of acute rheumatic fever.

SUMMARY

A case is reported in which the initial attack of acute rheumatic fever occurred at 65 years of age. The presenting clinical picture included generalized joint involvement, fever, leucocytosis, a markedly prolonged P-R interval, and a rapid sedimentation rate. There was an excellent response to salicylate therapy. This response included an abatement of the joint symptoms, toxicity, and fever; and a return to a normal leucocyte count, sedimentation rate, and P-R interval. The absence of any previous heart disease or joint pains, the persistently elevated

antifibrinolysin titer, the secondary anemia, the transient abnormalities in the electrocardiograms, and the murmurs which appeared during the attack and then disappeared with recovery all contribute to the diagnosis of an initial attack of acute rheumatic fever despite the advanced age of the patient.

REFERENCES

1. Leonard, M.: Puberty and Prognosis in Rheumatic Fever, Am. Heart J. **14**:192, 1937.
2. Juster, I. R.: The Significance of Rheumatic Activity in Chronic Rheumatic Heart Disease, Am. Heart J. **15**:1, 1938.
3. Cohn, A. E., and Lingg, C.: The Natural History of Rheumatic Cardiac Disease, J. A. M. A. **121**:1, 1943.
4. Juca, A., and White, P. D.: The Cause of Death in Rheumatic Heart Disease in Adults, J. A. M. A. **125**:767, 1944.
5. Rothschild, A. M., Kugel, M. A., and Gross, L.: Incidence and Significance of Active Infection in Cases of Rheumatic Cardiovascular Disease During Various Age Periods; Clinical and Pathological Study, Am. Heart J. **9**:586, 1934.
6. DeGraff, A. C., and Lingg, C.: The Course of Rheumatic Heart Disease in Adults, Am. Heart J. **10**:459, 1935.
7. Rakov, H. L., and Taylor, J. S.: Acute Rheumatic Heart Disease in The Aged, Am. Heart J. **2**:244, 1941.
8. Green, J. A., and Bennett, A. W.: Acute Rheumatic Heart Disease in The Aged, Am. Heart J. **30**:415, 1945.

Abstracts and Reviews

Selected Abstracts

Gomes, E. L., Capriglione, L., and de Souza, E. A.: Cardiac Changes in Uremia With Special Reference to Hyperpotassemia. Arq. de clin. **3**:151 (Sept.), 1947.

The electrocardiographic changes commonly noted in preterminal stages of hyperpotassemia were demonstrated in three uremic patients. All subjects revealed a marked decrease in urinary volume and alterations in potassium level that were not necessarily correlated with the severity of the electrocardiographic changes. These changes were of the usual type with marked alteration of the P waves and of the QRS complexes and with increased amplitude of the T waves. First degree heart block, sinus arrest, and cardiac standstill occurred preterminally. The clinical signs of hyperpotassemia consisted of paresthesias, flaccid paralysis, and acute left ventricular failure. In two necropsied cases no particularly striking alterations of the heart muscle were noted.

HECHT.

Schlesinger, P., and de Moraes, J.: The Clinical Value of the Esophageal Electrocardiogram. Arq. de clin. **3**:183 (Sept.), 1947.

The value of unipolar esophageal leads in conjunction with standard bipolar limb leads, unipolar limb leads, and precordial leads is demonstrated on twenty patients. The value of such leads in ventricular enlargement, in coronary insufficiency with and without myocardial infarction, and in auricular disorders is emphasized. The influence of position of the heart upon the auricular and ventricular pattern obtained has not been considered. A case of Chagas' disease with complete A-V heart block and an example of anomalous A-V conduction (Wolff-Parkinson-White syndrome) are included.

HECHT.

Winton, S. S.: Sinoauricular Block: An Analysis of Eleven Cases. Acta cardiol. **3**:108 (Fasc. 3), 1948.

Eleven examples of the disorder are discussed. All patients revealed signs of organic heart disease and four had received digitalis at the time the block was present. In two instances the block disappeared spontaneously; in one, following the administration of atropine. Three of the patients demonstrated an uncomplicated sinoauricular block, while five were classified as sinoauricular block with Wenckebach phenomenon. An additional case of the latter type could be converted to 2:1 sinoauricular block by carotid sinus pressure. Nodal escape, nodal rhythm, and reciprocal conduction from ventricle to auricle to ventricle ("sandwiching") was noted in the remaining two patients.

HECHT.

Evans, W., Dick, P., and Evans, B.: Rapid Digitalization. Brit. Heart J. **10**:103 (April), 1948.

Because there is no agreement on the best preparation and route of administration for inducing rapid digitalization, this study was designed to discover the most effective preparation for rapid digitalization, when given orally or intravenously, by comparing the effects on the same

patients of as many as possible of the following preparations: (1) strophanthin, (2) ouabain and K-strophanthosid, (3) Digoxin, (4) digitoxin, (5) lanatoside C, (6) digitalis leaf, and (7) tincture of digitalis.

Twenty patients with mitral stenosis or hypertension were selected. All had auricular fibrillation with a rapid ventricular rate and with slight to moderate congestive failure. All were on a normal hospital diet with fluids restricted. None had had digitalis for at least the preceding seven days. The order in which the drugs were given was deliberately varied from patient to patient. The consistency of the action of a drug in the same dosage and in the same patient was tested in only two individuals. In one instance, the effect was different and in the other, almost identical. In successive cases, however, the drugs produced the same result with remarkable consistency.

The fall in ventricular rate was regarded as the most satisfactory index of digitalization. A digitalis effect was classified as good when the fall in heart rate within four hours was 75 per cent of the maximal fall produced by any preparation in that patient, moderate when the fall in rate was between 50 and 75 per cent, and slight when below 50 per cent.

The authors found that strophanthin produced good effects only with a dose (1.0 mg.) which is larger than that generally regarded as safe. Strophosid (0.5 mg.) was superior to strophanthin yet did not produce the consistent results obtained from digitalis preparations and no justification was found for the continued use of either strophanthin or strophosid.

Digitalis nativelle, in a dose of 1.2 mg. orally, gave inconstant results and this dose was regarded as too small. No support was found for the contention that it is completely absorbed. Intravenously, a dose of 1.2 to 1.5 mg. gave consistently good results within two hours, which compared favorably with the results given by both Digoxin and lanatoside C, although the latter two frequently produced a more rapid effect in one hour.

The oral digitalization dose of Digoxin is regarded as at least 2.0 mg. and probably as much as 3.0 milligrams. Intravenously, the minimal full dose is regarded as 1.0 milligram. By this method, a good result was produced in most instances and a rapid effect in more than one-half. But it was inferior to lanatoside C in six of eight instances. Lanatoside C in a dose of 1.5 mg. produced a good effect in all instances.

When a digitalis effect is required within an hour, intravenous lanatoside C (1.5 mg.) or intravenous Digoxin (1.0 mg.) is recommended. When a digitalis effect is required within four hours, oral Digoxin (2.0 to 3.0 mg.) is recommended.

SOLOFF.

Dick, P.: The Relative Value of Digitaline Preparations in Heart Failure With Auricular Fibrillation. Brit. Heart J. **10**:122 (April), 1948.

This study was undertaken to ascertain whether there was any variation in the value of six commercial preparations of digitaline available in Great Britain when dispensed to patients with heart failure or auricular fibrillation. Thirteen patients were selected; three of these failed to complete the study. Two had hypertension and eight had mitral stenosis. With one exception, all had received powdered digitalis leaf for prolonged periods. A test period of fourteen days was used. The apical rate was counted for three successive half minutes. The order in which the preparations were given was deliberately varied. In order to check the results, a second series of trials on seven other patients was carried out.

One preparation was much less effective than the other five in both series. This may have been due to differences in the procedure for manufacture of digitaline.

It is suggested that until a standardized procedure for the manufacture of digitaline is introduced, digitalis leaf should be used for continuous digitalization.

SOLOFF.

Glasser, A.: The Normal Electrocardiogram and Its Relation to the Body Build. Cardiologia **12**:323 (Fasc. 6), 1947-1948.

Standard electrocardiograms of 193 healthy, robust, 23- to 58-year-old men were correlated with data of their body builds and a comparison has been made with similar series of tracings ob-

tained by other authors. A point is made of the fact that only leads taken simultaneously have been used for measurement. A P-R interval longer than 0.20 second was present in 3 per cent of the cases; there was no correlation of the duration of this interval with age. The mean angles α of the vectors were: of P, 45.5° (−13° to +80°); of R, 50.0° (−4° to +109°); of T, 38.7° (0° to +81°). The manifest value of R was larger in light than in heavy individuals. The ratio of vector T to vector R was greater in left than in right axis deviation.

The angle α of R was larger in tall, slender, and light men than in small, broadchested, heavy men. It decreased with age irrespective of blood pressure or type of body build. There was a definite inverse relation of this angle to the transverse horizontal square area of the thorax and a definite direct relation to the height of the thorax. An increase of 1.0 cm. in the latter was accompanied by an increase of 5° in the former. Age had no demonstrable influence on this angle. The left axis deviation type of the ventricular complexes displayed a smaller angle between the vectors R and T than the right axis deviation type.

BRUMLIK.

Polzer, K.: Rate and Rhythm in Acute Myocardial Infarction. Cardiologia **13**:1 (Fasc. ½), 1948.

Fifteen of fifty-one patients with acute myocardial infarction showed a temporary bradycardia during the first twenty-four hours caused by excessive sinus bradycardia, complete A-V block, or nodal rhythm. The author assumed that the response was of a reflex nature. However, most patients were under the vagal influence of large doses of morphine. The Q-T interval was usually prolonged over the predicted normal range.

HECHT.

Alvarez Mena, S.: The Normal Configuration of the Ensiform Lead (V_e). Rev. españ. de cardiol. **2**:1, 1948.

The configuration of 100 ensiform leads has been analyzed. When placed over the lower end of the xyphoid cartilage the electrode registers potential variations of the free wall of the right ventricle and of the adjacent interventricular septum. The pattern is similar to that obtained from other right ventricular regions.

HECHT.

Garcia, E., Arriba, O., and Lopez, F.: Diphtheria and Coronary Occlusion. Rev. españ. de cardiol. **2**:59 (July 31), 1948.

During the course of severe diphtheria in a 12-year-old boy a classical episode of myocardial infarction occurred on the fifth day of the disease. Characteristic electrocardiograms were obtained. As no other etiological factor could be implicated, the authors assume that an acute infectious arteritis of the coronary arteries had resulted in intravascular thrombosis. The patient died following this episode, but necropsy was not performed.

HECHT.

Calvino, J. M.: Obliterating Thrombosis of the Right Auricle. Report of Two Cases. Rev. cubana de cardiol. **1**:1 (Jan.), 1948.

The author presents the cases of two patients with heart disease whose clinical findings were characterized by dyspnea, paroxysmal in type, and typical signs of right heart failure. At necropsy, a pedunculated thrombus of the right auricle was found in each case. It was clear that some of the attacks of dyspnea, cyanosis, and right heart failure were due to obstruction of the tricuspid orifice by the freely movable thrombus.

The author reviews the literature and suggests that the diagnosis, if suspected during the life of the patient, may be confirmed by angiocardiography. Incomplete filling of the right auricle and narrowing of the valvular opening by the thrombotic mass may thus be demonstrated.

GOLD.

Malinow, M. R., Moia, B., Otero, E., and Garcia A.: Circulatory Changes Produced by Exercising Ischemic Muscle. I. Preliminary Observations. Rev. argent. de cardiol. **15**:1 (Feb.), 1948.

Standardized weight-lifting exercises (lifting of five-pound weights forty times per minute over 5.0 cm. for three minutes) were performed on five normal subjects. A slight increase in heart rate and in mean arterial pressure was noted. The pressure changes reversed themselves regularly and a fall in systolic and diastolic pressures occurred on recovery. Exercising of an ischemic limb resulted in a slightly higher rise of arterial pressure with a lessened tendency to an overswing of pressure values below the resting value. The heart rate increased as before. Atropine and ergonovine did not greatly alter the response obtained. The studies are preliminary to similar observations in patients with intermittent claudication and to studies on the pathogenesis of pain arising from an ischemic extremity.

HECHT.

Del Zar, L. E., and Bronstein, J.: The Influence of Infiltration Anesthesia of the Precordial Region on the Occurrence of Precordial Pain and on Electrocardiographic Changes in Angina Pectoris. Rev. argent. de cardiol. **15**:17 (Feb.), 1948.

Twenty or 40 mg. of 1 per cent procaine, given subcutaneously in the precordial area, prevented or attentuated the occurrence of precordial pain in seven of ten patients subjected to an exercise test. In eighteen patients the electrocardiographic changes on exertion were not altered by the procedure, even when pain was obliterated. A full explanation of the discrepancy is not given, but it appears unlikely that precordial procaine infiltration altered coronary blood flow, as has been suggested before.

HECHT.

Alzamora-Castro, V., Rubio, C. W., and Battilana, G. D.: The Systolic Murmur in Aortic Stenosis. Rev. argent. de cardiol. **15**:25 (Feb.), 1948.

Simultaneous registration of arterial pulse curves and phonocardiograms reveal that the systolic murmur of aortic and pulmonic stenosis begins at the onset of the ejection period and fades toward the latter part of systole. The maximal intensity of the murmur coincides with the maximal ejection period.

HECHT.

Etala, F., and Berreta, J. A.: Anatomical-Clinical Study of a Case of Post-tachycardial Syndrome. Rev. argent. de cardiol. **15**:133 (Feb.), 1948.

Cossio, González-Sabathié, Berconsky, and Vedoya, in three successive articles, have described a clinical picture which they called "post-tachycardial syndrome," based on the following data: (a) relatively young subjects, usually without demonstrable cardiac lesions; (b) repeated and prolonged attacks of paroxysmal tachycardia, mostly ventricular; (c) reversible cardiac enlargement; (d) electrocardiographic changes after the attack consisting of depression of the RS-T segment in one lead with elevation in another, inversion of the T wave, and prolongation of the Q-T interval; (e) gradual return of the electrocardiograph to normal within a few days; and, (f) at post mortem, the presence of a dilated and hypertrophied myocardium with absence of other lesions.

The authors report an additional case with post-mortem study. The histologic study failed to reveal any typical change in the myocardium or in the coronary system.

Even if the death in the reported case cannot be attributed with certainty to this syndrome, the latter cannot be considered as completely benign because it may be followed by sudden death or by heart failure.

LUISADA.

Stein, I. D., Harpuder, K., and Byer, J.: Effect of Sympathectomy on Blood Flow in the Human Limb. Am. J. Physiol. **152**:499 (March), 1948.

Plethysmographic studies in a small group of patients with various peripheral vascular diseases (thromboangiitis obliterans, arteriosclerosis, Raynaud's syndrome, cold injury, and essential hypertension) confirmed previous observations that sympathectomy fails to increase the resting blood flow within muscles, but does increase the skin circulation of the denervated extremity. The calf was used to test predominantly muscle blood flow, while the flow in the foot represented primarily skin circulation. Blood flow in muscles could be effectively increased by exercise, tissue heating, or release of temporary arterial occlusion. These procedures are known to release vasodilating metabolites. It is implied that sympathectomy will be useful clinically only for lesions or symptoms resulting primarily from deficient skin circulation.

HECHT.

Eckenhoff, J. F., Hafkenschiel, J. H., Foltz, E. L., and Driver, R. L.: Influence of Hypotension on Coronary Blood Flow, Cardiac Work, and Cardiac Efficiency. Am. J. Physiol. **152**:545 (March), 1948.

Hypotension was produced by the subdural injection of procaine hydrochloride or by the intravenous injection of tetraethyl ammonium chloride in anesthetized dogs whose coronary blood flow was being measured by the nitrous oxide method. Cardiac work and efficiency were calculated from venous catheterization data.

Diminished cardiac output with marked reduction in cardiac work accompanied the fall in blood pressure in seven of the eight experiments. Coronary blood flow declined in all instances (average, 25 per cent) but relatively less than cardiac work, which on the average fell 56 per cent. Cardiac efficiency, which is the work done divided by energy intake, declined 36 per cent. This would appear to indicate a decreased capacity of the heart to perform its work under these conditions, but evidence for such capacity is lacking, since the hypotension did not seem to be harmful to the experimental animal. The discrepancy is thought to lie in the concept of mechanical cardiac efficiency, the calculation of which fails to include the utilization of oxygen for factors other than actual mechanical work, such as the energy used for the maintenance of the cardiac muscle cells, or that required for isometric ventricular contraction. Cardiac efficiency, as calculated, is not a valid criterion of the heart's capacity for work under changing experimental conditions.

HECHT.

Galdston, M., and Steele, J. M.: Arterial Pressure Waves in a Patient With Coarctation of the Aorta. Am. J. Physiol. **152**:554 (March), 1948.

In addition to recording the usual arterial pressure pulse waves in an upper and lower extremity in a patient with coarctation of the aorta, the arterial tracing from a collateral artery connecting the arterial tree above and below the coarctation was recorded by the means of a Hamilton intra-arterial manometer. The pressure in the collateral vessel, the left subscapular artery, whose lumen measured 0.5 cm. in diameter, was 215/100. The pressure and the form of the pulse tracing were identical to those of the left radial artery although the collateral artery arose distal to the obstruction. The coarctation and the anatomical arrangement of the collateral circulation were confirmed by autopsy.

HECHT.

Lenel, R., Katz, L. N., and Rodbard, S.: Arterial Hypertension in the Chicken. Am. J. Physiol. **152**:557 (March), 1948.

Hypertension was consistently produced in chickens when saline solution was substituted for drinking water. After sixty days of saline intake the average systolic and diastolic pressures rose from the control average of 132/117 to an average of 182/154. Prompt fall in blood pressure followed withdrawal of the saline. The degree of hypertension was further increased by raising

of the salt concentration from 0.9 per cent to 1.2 per cent. Blood volume and hematocrit showed no significant changes.

Dehydration with loss of weight was the usual course of the chickens on the saline regime. No anasarca occurred except in one bird which died after forty-three days and showed pulmonary edema, pericarditis with effusion, and hyperemia of the other organs. After three months and two separate periods of salt ingestion, all of the chickens at autopsy showed hyperplasia and proliferation of glomerular tufts and Bowman's capsule with compression of the capillaries.

HECHT.

Campbell, W. N., Sokalchuk, A., and Penman, R.: Validity of T-1824 in Plasma Volume Determinations in the Human. Am. J. Physiol. **152**:563 (March), 1948.

The estimation of plasma volume by T-1824 was reinvestigated in six subjects under basal conditions. Two injections of the dye were made at a thirty-minute interval, and blood samples drawn at ten, thirty (prior to second injection), and forty minutes. Calculations of the plasma volume on the ten-minute samples after each injection showed an average difference of but 1 per cent. This suggested that the dye method gave reliable results and that, if active removal of the dye during the early mixing period by the reticuloendothelial system occurs in man, it does not invalidate the determinations. That complete mixing of the dye had occurred at ten minutes was shown by the close agreement between the samples drawn simultaneously from each arm.

HECHT.

Sussman, A. H., Hemingway, A., and Visscher, M. B.: Importance of Pressure Factors in the Genesis of Pulmonary Edema Following Vagotomy. Am. J. Physiol. **152**:585 (March), 1948.

The problem of the production of pulmonary edema in guinea pigs maintained on positive pressure artificial respiration was reinvestigated. Previously it had been reported that fatal lung edema occurred in vagotomized animals, but not in those with intact vagi. The authors found that neither group of guinea pigs developed pulmonary edema when the insufflation pressure was 6 mm. of mercury. At a pressure of 20 mm. Hg, however, massive edema occurred in all animals. Thus, no evidence was found to indicate that vagotomy has any effect on the pulmonary vascular system favoring edema.

HECHT.

Surtshin, A., Rodbard, S., and Katz, L. N.: Inhibition of Epinephrine Action in Severe Hypoxemia. Am. J. Physiol. **152**:623 (March), 1948.

Severe hypoxemia was produced in anesthetized dogs by artificial respiration with 100 per cent nitrogen. The arterial pressure gradually increased for sixty to ninety seconds, but then fell rapidly. If the breathing of nitrogen was continued, death shortly ensued from circulatory failure, cardiac dilatation, and arrest in diastole.

When normal air breathing was instituted during the phase of hypoxemic pressure fall, the blood pressure promptly rose to levels above the hypoxemic pressure rise. This was attributed to the accumulation of pressor substances which fail to act in the absence of oxygen. When epinephrine was injected intravenously or intracardially during the hypoxemic depression, the usual pressor response was absent or markedly diminished until after air breathing was reinstituted, at which time the adrenalin effect was superimposed upon the usual posthypoxemic pressor effect. Thus, the effect of epinephrine seems to depend on oxygenation of the blood. It is implied that the clinical use of epinephrine in cases of marked hypoxemia is of no avail unless oxygenation of the blood has been accomplished.

HECHT.

Campbell, G. S., and Harvey, R. B.: Postural Changes in Vital Capacity With Differential Cuff Pressures at the Bases of the Extremities. Am. J. Physiol. **152**:671 (March), 1948.

Vital capacity has been shown to decrease in changing from the standing to the recumbent position. The authors found a decrease of 185 c.c. in nine normal male subjects. When blood was

progressively pooled in all the extremities by cuffs inflated to the diastolic level, the decrease in the recumbent position was nullified. When the volume of blood in the extremities was kept constant by cuffs inflated to the systolic level, there was no change in vital capacity.

HECHT.

Froment, R., and Gallavardin, L.: Sinus Arrest With Intermittent Nodal Rhythm. Arch. d. mal. du coeur **41**:113 (March), 1948.

Electrocardiograms of a 55-year-old man are presented which over a four-year period demonstrated a peculiar arrhythmia. Careful analysis of many records reveals the coexistence of a sinus rhythm (rate 70) and an A-V nodal rhythm. Frequently shorter and longer periods of intrinsic arrest of the impulse formation within the sinus node were observed which were regularly compensated for by the slower nodal rhythm. When the activity of the nodal center decreased, the sinus recommenced its activity. The sinus pauses could clearly be differentiated from ordinary sinoauricular block and were accentuated by vagal stimulation. The patient did not reveal any clinical symptoms or signs of heart disease.

HECHT.

Paterson, J. C., Slinger, S. J., and Gartley, K. M.: Experimental Coronary Sclerosis. I. Medial Degeneration as the Primary Lesion in Coronary Sclerosis of Cockerels. Arch. Path. **45**:306 (March), 1948.

The authors report on the occurrence of a medial lesion which they consider to be of prime importance in the genesis of coronary sclerosis in chickens. They found that the incidence of coronary sclerosis in cockerels was the same whether or not dry cholesterol was added to their diet. The addition of cholesterol, however, accelerated the sclerotic process already established. They also found that a degenerative medial lesion preceded the intimal changes in treated and control cockerels.

The majority of control birds showed spontaneous arteriosclerosis, the most important change being in the media. The feature of this lesion was a hydropic degeneration with disruption of the elastica; a total lack of calcification sets this avian lesion aside from medial changes in other species. Round cell infiltration in the adjacent adventitia and some slight fibroblastic thickening in the overlying intima complete the picture of spontaneous coronary sclerosis as seen in these chickens.

Cholesterol feeding did not alter the incidence of this arterial degeneration, but added significantly to the intimal thickening, resulting in prominent foam cell aggregations, filled with lipoid material. These cells infiltrated the areas of medial hydropic degeneration and also the adventitial thickening, obscuring all other details by the formation of a nodular foam cell mass, sharply demarcated from the rest of the arterial circumference, and pouching inward into the lumen and outward beyond the normal adventitial confines. With massive foam cell infiltration, small points of calcification appeared.

The authors are unable to explain the pathogenesis of spontaneous arteriosclerosis in chickens. It involves the coronary arteries predominantly, and is often accompanied by a focal round cell infiltration of the myocardium, suggesting that infection may be the basis for the combined arteriomyocardial disease. The lesion is admittedly different from human atherosclerosis.

GOULEY.

Guenther, B., and Garcia Campo, M.: New Aspects of the Problem of Pressure Reactions. Rev. argent. de cardiol. **15**:53 (March-April), 1948.

The authors suggest that evaluation of the reactivity to "cold pressor" tests be based on the ratio of rise in pressure to basal pressure. A pressure reaction of more than 20 per cent is considered excessive. This maximal limit is compared with the pressure volume curves of the aorta given by Bazett and a correlation between the two is found. By applying this concept, the authors find that hyperreaction is as frequent in normal subjects as in hypertensive patients.

LUISADA.

Post, R. S., Visscher, P. H., and Wiggers, C. J.: Sequential Changes in Oxygen Consumption During Oligemic and Normovolemic Shock and Their Meaning. Am. J. Physiol. **153**:71 (April), 1948.

In standardized hemorrhagic shock in dogs, reduction in oxygen consumption is not a necessary concomitant of the irreversible state. Oxygen consumption, however, is drastically reduced immediately after the fall in arterial pressure. This remains low despite increased pulmonary exchange. Reinfusion of blood after irreversible circulatory changes have taken place resulted in a decided increase in the oxygen uptake over the normal values (average, 61 per cent). The early reduction in oxygen uptake following a large volume of blood loss is most likely secondary to the lowered cardiac output and lowered capacity to transport oxygen. The recovery of oxygen uptake during the latter part of the irreversible hypotensive period can be accounted for by the excess oxygen required for augmented respiratory activity. The large increase in oxygen consumption which follows a transfusion and continues even as circulatory failure redevelops is attributed to the combination of improvement in oxygen transport, continuance of augmented respiratory action, and oxidation of metabolic acids. The generally accepted hypothesis that irreversible circulatory changes are accompanied by reduced oxygen utilization is not conclusively supported by these and by other published observations.

HECHT.

Stacy, R. W., Whitehorn, W. V., and Hitchcock, F. A.: Susceptibility of Cats and Dogs to Progressive Anoxia. Am. J. Physiol. **153**:87 (April), 1948.

In a comparative study of the responses of cats and dogs under barbiturate anesthesia to anoxic anoxia, it was found that dogs were able to withstand low oxygen saturation better than cats. The dogs hyperventilated to a much greater degree than the cats. Denervation of the chemoreceptors prevented hyperventilation, obliterated any species differences, and further reduced the anoxic tolerance of both cats and dogs. It would appear, therefore, that the cells of the medullary respiratory center are equally susceptible to anoxia. The increase in arterial pressure during anoxia is reversed in both species following chemoreceptor denervation. A theoretical expression of the relation between volume of ventilation and the inspired air is presented.

HECHT.

Hoff, H. E., and Nahum, L. H.: Comparison of the Electrocardiographic Changes Produced by Heating and Cooling Epicardial and Endocardial Surfaces of the Dog Ventricle. Am. J. Physiol. **153**:176 (April), 1948.

Studies were carried out in eighteen dogs designed to determine the changes in direction of the T waves in the standard and precordial leads after warming and cooling of restricted areas of the endocardium and the overlying epicardium of both the right and left ventricles. Both endocardial and epicardial leads demonstrated an increase in the amplitude of the T waves when either the endocardial or the epicardial regions were heated. All leads showed inversion of T when either surface was cooled. The authors insist that their experiments lend no support to the theory that differences in rate of repolarization between epicardial and endocardial myocardium are responsible for the shape of the T wave, but they concede that T-wave inversion in precordial leads indicates repolarization delay in regions adjacent to the exploring electrode, while upright T waves signal delayed repolarization of distant regions.

HECHT.

Stoner, H. B., and Green, H. N.: Bodily Reactions to Trauma. The Effect of Ischaemia on Muscle Protein. Brit. J. Exper. Path. **29**:121 (April), 1948.

The authors were interested in studying the possible changes in muscle proteins which might be produced by ischemia. For this purpose they determined the amino acid content of the gastrocnemius and adductores muscles of the albino rat. Muscle ischemia was produced by means of metal clamps applied to the hind limb of the intact animal under ether narcosis. The

results were compared with those obtained on autolytic muscle of rats which were sacrificed and allowed to remain in the same environmental conditions as the "clamped" rats.

The results indicated that proteolysis, as judged by an increase in amino acid content, occurred in muscle deprived of the major part of its blood supply. The amount was much greater in ischemic than in autolysing muscle, the difference being considered to be related to the higher temperature of ischemic muscle. For the first hour after removal of the clamp, proteolysis occurred at an even greater rate than during the period of ischemia. It was felt that this was due to the fact that at this time there was a further increase in temperature in the muscle while the pH was still low. The second phase of protein breakdown did not commence until about three days after the period of ischemia and continued for the next four days. The pH conditions at this time were not suitable for the action of the tissue cathepsins, and the enzymes producing this proteolysis were probably derived from the leucocytes which infiltrate the damaged muscle.

ABRAMSON.

Sziberth, K.: Endangiitis Obliterans: A Contraindication to Stomach Resection. Wien. med. Wchnschr. **98**:160 (April), 1948.

A 37-year-old man who had been subject to increasing intermittent epigastric pains for five years showed diminished pulsations in peripheral arteries and radiological signs of a duodenal ulcer. A stomach resection was carried out. However, on the day which followed the operation the patient died. Autopsy revealed the cause of death to have been multiple hemorrhagic infarctions of the small intestine on the basis of mesenteric endangiitis; the peripheral arteries and the left coronary artery showed similar changes. The symptomatology of this relatively rare picture, its diagnosis, and implications concerning surgical decisions are discussed.

BRUMLIK.

Lenegre, J., Kilaidonis P., and de Brux, J.: Calcification of the Ascending Aorta. Arch. d. mal. du coeur **41**:193 (May), 1948.

Of thirty cases with calcification of the ascending portion of the aorta, twenty were known to have syphilis although only nine were seropositive at the time of the examination. Calcified syphilitic aortitis is in general better tolerated than aortitis without calcification. The rigidity of the aorta does not seem to play a part in left ventricular failure in aortic lesions. Calcification of the aorta must be considered a valuable sign of syphilitic aortitis which has become stationary and nonprogressive.

HECHT.

Braham, J., and Howells, G.: Hereditary Oedema (Milroy's Disease). Brit. M. J. **2**:830 (May 1), 1948.

The author discusses Milroy's disease, which is characterized by edema which is usually present in infancy or childhood and always by adolescence. The edema usually begins in the foot but never extends above the inguinal ligament. At first it is of the pitting type but later it becomes brawny. It affects one or both lower limbs. There is no known successful treatment other than possibly the Kondoleon operation; however, this disease is compatible with a long, nondisabling life. The familial hereditary background is necessary for diagnosis, but possibly there are some cases seemingly without this requirement, as this characteristic may skip a generation. Extant material for pathological study is limited to one biopsy which showed condensation of the superficial dermal papillary layer with hyalinization.

The author describes the case of a nineteen-year-old boy who complained of a nondisabling swelling of the right leg which began at age seventeen. One sister was similarly affected. There were no trophic lesions. Laboratory examinations were normal. No treatment was advised other than elastic bandages.

WAGNER.

Kumpe, C. W., and Bean, W. B.: Aortic Stenosis: A Study of the Clinical and Pathologic Aspects of 107 Proved Cases. Medicine **27**:139 (May), 1948.

The authors report the clinical and morphological aspects of 107 proved cases of aortic stenosis uncomplicated by deforming lesions of other valves. About three-fourths of the cases were men. A positive history of acute rheumatic fever was obtained in two-thirds of the cases. The cases were divided into two groups on the basis of symptoms and the course of the disease. Group 1 included those whose major complaints were related directly to the heart and those in congestive heart failure. Group 2 included those whose major complaints were not directly related to the heart. Of the seventy-eight patients in Group 1, thirty-four had chronic congestive failure, ten had intermittent bouts of failure, and nineteen had an abrupt onset of failure shortly before they were admitted. The blood pressure was not characteristic. There were a number with systolic hypertension and others with low diastolic pressures, but relatively few with the low systolic and the low pulse pressure described as typical of aortic stenosis. The second aortic sound was usually absent or much reduced in intensity. Occasionally a second sound heard at the aortic area was loud and must have been transmitted from the pulmonic valve. A systolic murmur was heard at the base in only 83 per cent of the patients, this murmur being transmitted into the vessels of the neck in slightly less than one-half of those in whom it was heard. Basal diastolic murmurs were heard in one-third of the patients. Apical systolic murmurs were heard in 82 per cent of the patients and an apical diastolic murmur was heard in slightly less than one-third. Thrills were felt in thirty-three patients. The systolic murmurs and thrills were related in intensity to the degree of stenosis, but they were absent in several cases of severe valvular obstruction. Fluoroscopic demonstration of calcified aortic valves verified the diagnosis five times. The electrocardiogram was not pathognomonic.

Cardiac pain occurred in 37 per cent of the patients before hospitalization and in 8 per cent while under observation. It differed from typical angina pectoris in its lack of radiation or its radiation to the right, its advent after, rather than during, exercise and its refractoriness to nitroglycerin. It was much more closely associated with severe aortic stenosis than with coronary arteriosclerosis.

The hospital course was characterized by signs of congestive failure unusually refractory to treatment with digitalis, oxygen, or diuretics. Episodes of sweating, cyanosis, restlessness, and confusion occurred in twenty-eight patients. Signs and symptoms referable to the brain were conspicuous in thirteen patients. The authors differentiated the type of sudden death which ended the life of 21 per cent of their patients from instant syncopal death and unexpected death where the terminal stage lasts for hours. In their material sudden death occurred in a matter of minutes, usually between five and thirty. In contradistinction to those with instant death following myocardial infarction, a history of syncopal attacks was not common in those bedfast patients who died suddenly.

The lesions of aortic stenosis were graded into three classes on the basis of severity. In every valve calcium was found grossly or histologically and it varied in quantity with the severity of the lesion. In severe lesions the coronary ostia were distorted. Fusion of cusps and nodule formation were common. The hearts were enlarged in the majority of cases and the heart weight was related to the extent of valvular obstruction. Coronary arteriosclerosis was common, and had given rise to thrombosis and myocardial infarction in an appreciable number of cases. The clinical diagnosis was made in only 24 per cent of all cases, reflecting both unfamiliarity with the diagnostic criteria and too great acceptance of the classic triad of basal systolic murmur, thrill, and small, slowly rising pulse.

KLINE.

McCall, M.: Dicumarol Therapy in Acute Coronary Occlusion With Myocardial Infarction. Am. J. M. Sc. **215**:612 (June), 1948.

Dicumarol was used as the sole anticoagulant in the management of seventy-one patients with myocardial infarction following acute coronary occlusion. No effort was made to compile statistical data on these patients. Gross hematuria occurred on three occasions and was readily controlled by the intravenous administration of 60 mg. of menadione bisulfite. Unexplained

difficulty was encountered in the maintenance of the desired prothrombin time in twenty-one patients. Nine deaths in the group gave a mortality of 12.7 per cent. Six were due to heart failure, and one each to rupture of the ventricle, pulmonary embolism, and extension of the infarction. It is emphasized that a daily prothrombin determination is mandatory for successful therapy. The author concludes that continued use of this form of therapy is justified by the resultant low incidence of thromboembolic phenomena, which insures a less stormy convalescent period.

DURANT.

Reich, C., and Eisenmenger, W.: Further Studies on the Anticoagulants. Am. J. M. Sc. **215**:617 (June), 1948.

This report embodies a continuation of studies on Dicumarol and heparin initiated at Lenox Hill Hospital in 1943. In the present series of 300 cases, the patients were divided into four main groups: (1) patients with postoperative cases treated prophylactically with anticoagulants to prevent thrombotic complications; (2) patients with active venous thrombosis; (3) patients with acute embolic episodes, usually pulmonary; and (4) patients with coronary thrombosis.

There were about 200 patients in the first group, at least 50 per cent being women who had had pelvic operations. The treatment in this group was with Dicumarol, which was started two to four days postoperatively and maintained until the patient was ambulatory. The results were most satisfactory, and it is possible to practically guarantee the prevention of postoperative thromboses in patients so treated. In the third group, there were thirty patients, twenty-six of whom had pulmonary emboli. Combined heparin and Dicumarol therapy was used. There were two deaths, and one other patient had a nonfatal pulmonary embolus while on anticoagulant therapy. As a result of experience in this group, it is suggested that if surgery is contemplated while a patient is on Dicumarol therapy, 120 mg. of vitamin K be injected intravenously a few hours preoperatively.

The second group included forty-five patients with thrombophlebitis, twenty of whom were postoperative patients who had received no preoperative anticoagulant treatment. Dicumarol was used without heparin in this group. In none of these patients were there any pulmonary emboli. When therapy is used promptly in this group the thrombosis can be restricted to just one segment of the vein and often the collateral circulation is sufficient to prevent lymphatic stasis.

In the fourth group there were thirty patients with coronary artery disease, twenty-four of whom were typical examples of coronary occlusion with myocardial infarction. Of these, four died; two of progressive failures, one after having shown clinical and electrocardiographic evidence of progressive myocardial damage, and one in what seemed to be a new acute coronary episode. While this group is too small to present any definite conclusions, the impression is given that the main usefulness of anticoagulant therapy in coronary artery disease is in the prevention of embolization either from peripheral veins or cardiac mural thrombi.

It is pointed out that there may be an increased sensitivity to Dicumarol in cases of congestive failure, possibly because of the decreased renal blood flow with retention of Dicumarol.

DURANT.

Starr, I., and Mayock, R. L.: On the Significance of Abnormal Forms of the Ballistocardiogram. A Study of 234 Cases With 40 Necropsies. Am. J. M. Sc. **215**:631 (June), 1948.

The various types of abnormalities of ballistic form are described. The form may vary from beat to beat, or it may vary with respiration so that in many cases no one type of complex predominates. In other cases one type of abnormality does predominate, but there is usually some beat-to-beat variation.

Abnormalities of ballistic form were encountered most frequently in the cases in which there was manifold evidence of heart disease, or in conditions such as hypertension and hyperthyroidism in which heart disease is a frequent complication. They were found with great frequency in cases in which structural abnormalities of the heart were later demonstrated at necropsy. Never-

theless, ballistic abnormalities of form were encountered in fifty-eight cases in which no cardiac abnormality had been suspected and in eight cases in which the heart was essentially normal at necropsy.

It is concluded that an abnormality of ballistic form indicates an important type of cardiac dysfunction, the manifestation of an abnormal manner of contraction. This functional abnormality is usually associated with well-known kinds of structural abnormality, but it has also been found quite frequently when cardiac disease was not detected by the routine clinical tests now in use.

DURANT.

Tamagna, I. G., and Poindexter, C. A.: A Comparative Evaluation of Tetraethylammonium Chloride and Sodium Amytal in Patients With Hypertensive Cardiovascular Disease. Am. J. M. Sc. **215**:651 (June), 1948.

Tetraethyl ammonium chloride when compared with sodium amytal appears to be a safe and more specific agent for the preoperative evaluation of hypertensive patients. Results are obtained within thirty minutes, as compared to five hours with sodium amytal. The patient is awake throughout the test, whereas he is subjected to a day of drowsiness from sodium amytal. There is marked parallelism in the drop in blood pressure in both tests.

DURANT.

Soloff, L. A., and Bello, C. T.: "Capillary Fragility" in Hypertension: The Effect of Antiscorbutic Therapy on Results of Tests for "Capillary Fragility." Am. J. M. Sc. **215**:655 (June), 1948.

The capillary fragility of fifty hypertensive patients previously saturated with vitamin C for one month was determined by the Göthlin and Rumpel-Leede tests. Only two patients had a positive Göthlin test, while thirty-three had a positive Rumpel-Leede test. This is in contrast to the studies of Griffith and Lindauer in which 18 per cent of hypertensive patients were found to have a positive Göthlin test. The authors believe that the administration of vitamin C in their series may have prevented the appearance of a positive reaction to this test in most of their cases, and suggest the need for a re-evaluation of this test on a large series of patients previously saturated with this vitamin. They also suggest that the incidence of subclinical scurvy in hypertensive patients may be higher than in the group of normal students studied by Bell, Lazarus, and Munro.

The authors found that Rutin did not reverse to normal the Göthlin test of the two patients with abnormal reaction, nor did it reverse to normal the Rumpel-Leede test in the thirty-three patients with a positive reaction to this test. There did not appear to be any correlation between retinal hemorrhages and a positive Rumpel-Leede reaction.

DURANT.

Soloff, L. A., and Bello, C. T.: The Relationship of Retinal Hemorrhages in Hypertensive Patients to Cerebral Hemorrhage. A Comparison of the Retinal Picture in Hypertensive Individuals Who Died of Heart Failure With Those Who Suffered a Cerebral Hemorrhage. Am. J. M. Sc. **215**:660 (June), 1948.

Retinal hemorrhages occurred in fourteen (77 per cent) of eighteen patients with hypertension who died of cardiac failure without cerebral hemorrhage. They occurred in five (29 per cent) of seventeen patients with hypertension who suffered a cerebral hemorrhage. An analysis of the retinal picture found in the cases studied revealed the fact that a marked degree of spasm, usually with Grade 2 sclerosis, is necessary for the production of retinal hemorrhages. The spasm is apparently of importance in producing an extra burden on the heart or kidneys and thereby producing failure of either or both of these organs. Apparently, if this is not correctable, the patient does not live long enough to suffer a cerebral hemorrhage.

The study therefore indicates that retinal hemorrhages cannot be used as a prognostic sign of future cerebral hemorrhage, as they occur more frequently in those who ultimately die of cardiac or renal failure without a massive cerebral accident.

DURANT.

Unterman, D., and DeGraff, A. C.: The Effect of Exercise on the Electrocardiogram (Master "Two-Step" Test) in the Diagnosis of Coronary Insufficiency. Am. J. M. Sc. **215**:671 (June), 1948.

The Master "two-step" exercise test was performed in 163 subjects, including controls, patients with heart disease, and patients convalescing from acute illness. The electrocardiographic changes following exercise were regarded as significant in 40.7 per cent of fifty-nine patients with coronary disease and in 48.3 per cent of thirty-one patients with the anginal syndrome. No serious untoward reactions to exercise were noted. The electrocardiographic response was positive in seven of ten patients who experienced anginal manifestations during the test. A small number of patients with a negative "standard" test showed a positive test when the "double standard" exercise was performed.

The test provides a means of determining coronary insufficiency when other means are not available, although it does not do so in all cases. The practical value of the test appears to be limited by a high incidence of negative responses. The theoretical aspects of the test are discussed. The possible influence of different electrocardiographic techniques and criteria, as well as the influence of food, digitalis, and recent acute illness, is considered.

DURANT.

Bailey, W. H.: Air Embolus in Pneumoperitoneum. Report of a Fatal Case. Am. Rev. Tuberc. **57**:621 (June), 1948.

The patient was admitted to the hospital with a diagnosis of pulmonary tuberculosis with endobronchial involvement. The initial pneumoperitoneum was instituted with no untoward results. The first refill, in which the air embolus occurred, took place twelve days later.

After twice verifying the fact that the point of the needle was in the peritoneal cavity the manometer tube was connected to the needle and a fluctuation of zero plus one was obtained. The air, flowing freely, was permitted to enter the peritoneal cavity under gravity. When 100 c.c. of air had been introduced, the reading was still zero plus one. The patient noticed no unusual reactions. Just when the 300 c.c. mark was reached, the patient stated that he felt dizzy. The needle was withdrawn; two seconds later the patient had a general convulsion and was given 1.0 c.c. of adrenalin. By this time the patient had lost consciousness, but respiration and pulse continued. He was given 2.0 c.c. of adrenalin intravenously, followed by artificial respiration and oxygen, and 5.0 c.c. of Coramine intravenously. The patient expired fifteen minutes after the refill was started and thirteen minutes after the onset of dizziness. Autopsy and microscopic examination of the internal organs failed to reveal the exact route of the air. On gross section of the heart, numerous small air bubbles were visible on the outer superior surface of the parietal pericardium. When the heart cavities were opened, a large quantity of frothy blood and stringy clot was found in the right auricle and ventricle. No air bubbles were found in the left side.

The author concludes that in inducing artificial pneumoperitoneum all technical details of injecting the air must be strictly followed. The injection should proceed very slowly at first, and the patient should be watched carefully. If the patient complains of any unusual sensations the injection should be stopped at once.

BELLET.

Wallis, A. D.: The Relation of the Cardiac Lesions of Rheumatoid Arthritis to Those of Rheumatic Fever. Ann. Rheumat. Dis. **7**:97 (June), 1948.

It is the author's purpose to propose that in rheumatoid arthritis, cardiac lesions indistinguishable from those of rheumatic fever are produced by tissue response to the union of sessile antibody and fresh antigen, the latter being necessarily homologous to the sessile antibody but presumably different from the antigen in rheumatic fever. The mechanism of production of cardiac lesions is the same in the two diseases, but the antigens are different.

The *Streptococcus hemolyticus* is a causative factor in rheumatic fever but not in rheumatoid arthritis. The relation of scarlet fever and hemolytic streptococcic sore throat to acute rheumatic

fever and the prophylaxis of acute rheumatic fever by sulfonamides are well established. The extraordinary prolongation of the active stage of the joint lesions of rheumatoid arthritis, their tendency to symmetry, and their indifference to sulfanilamide and penicillin may be cited as evidence against a streptococcal etiology for this kind of arthritis. Whatever the substance eventually to be found serving as antigen in rheumatoid arthritis, the evidence indicates that it is not a streptococcal derivative.

In the cases reported by Baggenstoss and Rosenberg, rheumatic-type heart disease was found in the autopsy study of sixteen of twenty-two cases of frank rheumatoid arthritis, an incidence of 72 per cent as compared with the over-all incidence of five per cent found at the Mayo Clinic. I nonly two of these sixteen cases had a history of rheumatic fever been obtainable. It was noted tha t cardiac damage tends to be less severe in rheumatoid arthritis than in classical rheumatic fever and it is suggested that this difference might result from the fact that the onset of rheumatoid arthritis is later than the onset of rheumatic fever.

The concept of sensitivity reactions in rheumatoid arthritis also furnishes an explanation of the presence of focal collections of round cells in the peripheral nerves and skeletal muscles in this disease. It seems likely that these cell collections have the same origin as the cardiac lesions which are under discussion, namely, the result of union of fresh circulating antigen with homologous sessile antibody. Fresh antigen enters the circulation more frequently, over a longer period, and probably in smaller amounts in rheumatoid arthritis than in rheumatic fever, and also the "sensitivity lesions" are more likely to leave permanent recognizable scars in the heart than in the peripheral nerves.

BELLET.

Johnson, J., and Kirby, C. K.: The Surgical Treatment of the Infantile Type of Coarctation of the Aorta. Ann. Surg. **127**:1119 (June), 1948.

The authors describe the two types of coarctation of the aorta. One is the adult type, which is short and occurs in the region of the ligamentum arteriosum; the other is the infantile type, which is long (4 to 5 cm.) and occurs in the region of the isthmus of the aorta. They point out that the adult type is effectively treated by resection of the stenotic area and restoration of continuity by end-to-end suture anastomosis, as described by Crafoord and Gross. However, the infantile type is not susceptible to an end-to-end anastomosis because of the long gap produced by the removal of the stenosed portion of the aorta. In three patients the authors were able to bridge this gap by using the left subclavian artery and carrying out an end-to-end anastomosis between it and the descending aorta.

The first patient, a 13-year-old boy, was restored to normal, whereas the second patient, a 17-year-old boy, was helped somewhat. The third patient, a 20-year-old man, died twelve hours after operation as a result of a rupture of the subclavian artery due to advanced arteriosclerotic changes in the vessel. The authors suggest that the ideal time to operate on these patients would be between the ages of 12 and 14 years.

LORD.

Samson, P. C.: Battle Wounds and Injuries of the Heart and Pericardium: Experiences in Forward Hospitals. Ann. Surg. **127**:1127 (June), 1948.

Samson discusses the problems associated with the management in forward hospitals of cardiac injuries occurring during warfare. There were three chief types of injuries: contusion of the ventricular wall, laceration of the ventricle or auricle, and retained foreign bodies either in the muscle of the heart or within the chamber of the heart. Pericardial injuries consisted of foreign bodies, hemopericardium, and lacerations of the pericardium.

The author emphasizes many diagnostic features of cardiac injury; he points out that the most significant was the clinical picture of cardiac dysfunction (persistent dyspnea, tachycardia, arrhythmia, etc.), which was out of proportion to the patient's obvious injuries.

Samson states that contusions of the heart are nonsurgical and should be managed like coronary occlusion, in that surgical procedures for other injuries should be delayed if possible for at least forty-eight hours. Early operation on patients with a contusion of the heart usually ended

fatally. Lacerations of the heart should be sutured if the patient's condition warrants and the pericardium drained into the left pleural space. In general, foreign bodies in the pericardium, in the myocardium, or in the chambers of the heart should be removed, but the mortality is considerably less if the operation can be postponed until the patient returns to a base hospital. Occasionally a foreign body embolus caused injury to the myocardium so that early surgical intervention was necessary.

The author discusses several points in regard to surgical technique which had proved to be of value in the management of cardiac injuries.

LORD.

Scott, M. R. A.: Weight and Blood Pressure. Brit. M. J. **2**:1195 (June 19), 1948.

A review of weights and blood pressures of an office staff, all men, was undertaken. This staff numbered 1,200 in 1938, 400 in 1943, and 600 in 1946. The group was examined in 1938-1939, 1943, and 1946-1947. The average age of the group varied considerably at different examinations: in 1938 the largest number was in the twenty six- to forty-year group, while in 1946, the sixteen- to twenty-year group was largest. The average weight in 1938 was 155 pounds, fully clothed; in 1943 it fell to 151 pounds and rose to 156 pounds in 1946.

It was found that up to the age of 40 years, men examined in 1946-1947 were on the average heavier than men of the same age in 1938-1939. In men from 41 to 55 years of age there was little difference in weight in the two periods. The men between 21 and 35 years who had been in the Armed Forces were on the average heavier than those who had not been.

The average diastolic pressures of all age groups in 1946-1947 were above those of 1938-1939, the maximum difference being 12 mm. Hg in the group between 41 and 45 years of age. Diastolic pressures were highest in 1943, probably reflecting war-produced anxiety. The average systolic pressures of all age groups in 1946-1947 were above those of 1938-1939, the maximum difference being 27 mm. Hg in those between 46 and 50 years of age. The rise in blood pressure can be correlated with a recent increase in neurocirculatory disorders in the staff over 50 years of age.

WAGNER.

Handelsman, J. C., Bing, R. J., Campbell, J. A., and Griswold, H. E.: Physiological Studies in Congenital Heart Disease. V. The Circulation in Patients With Isolated Septal Defects. Bull. Johns Hopkins Hosp. **82**:615 (June), 1948.

The authors report five cases with various types of septal defects and discuss the underlying physiologic principles relating to and the methods used in eliciting the disturbances observed in these conditions. The Fick principle was applied to determine the blood flow through various parts of the circulation. The following formulas were used:

$$\text{Systemic blood flow (ml. per minute)} = \frac{O_2 \text{ uptake (ml. per minute)} \times 100}{O_2 \text{ content of peripheral arterial blood (volumes per cent)} - O_2 \text{ content right auricular blood (volumes per cent)}}$$

$$\text{Pulmonary artery flow (ml. per minute)} = \frac{O_2 \text{ uptake (ml. per minute)} \times 100}{O_2 \text{ content of pulmonary vein blood (volumes per cent)} - O_2 \text{ content pulmonary arterial blood (volumes per cent)}}$$

$$\text{Shunt (ml. per minute) right-to-left} = \text{systemic flow} - \text{pulmonary artery flow}$$

$$\text{Shunt (ml. per minute) left-to-right} = \text{pulmonary artery flow} - \text{systemic flow}$$

The calculation of systemic flow was complicated by reciprocal admixture through an auricular septal defect. This necessitated the use of the oxygen content of blood from the superior vena cava as representative of mixed venous blood. This may provide an error in the results, since it has been shown that true mixture of venous blood does not occur before the outflow tract of the right ventricle.

As part of the physiological studies conducted in this group, three of the patients performed the standard exercise test. In all, there was a rise in the oxygen consumed per liter of ventilation. This finding is in contrast to the results obtained in the study of patients with the tetralogy of Fallot. In these latter there was generally a fall in the ratio of oxygen consumed per liter of ventilation during exercise. Conversely, in the present group under study, as in normal individuals and in patients with Eisenmenger complex, the rise in oxygen consumed per liter of ventilation during exercise demonstrated that the effective pulmonic blood flow can increase significantly with exercise.

Three patients had shunts from left to right and two had right- to left-shunts. In these two latter patients cyanosis was marked and the oxygen saturation of the peripheral arterial blood was low.

Pulmonary factors concerned with oxygen transfer in the lung are apparently not involved in this decrease in the saturation of peripheral arterial blood. In sixteen patients in whom it was possible to catheterize the pulmonary vein, the blood returning to the heart from the lungs was fully saturated. The finding, in two of these cases, that the shunt was predominantly directed to the left, implies an increase in the resistance of the pulmonary vascular tree. Evidence of increased resistance in the pulmonary vascular circuit is furnished by four findings: (1) intracardiac shunting of blood from right to left; (2) the presence of pulmonary arterial hypertension; (3) the marked loss of pressure head in the pulmonary circulation which became apparent when resistance in the pulmonary circuit was calculated; and (4) the changes in the ratio, velocity energy/total work, of the two ventricles.

In the light of the observation that normally pulmonary resistance is low, the assumption may be ventured that the increase in pulmonary resistance results from changes in the pulmonary vascular tree in the form of widespread sclerotic changes affecting the smaller blood vessels possibly in combination with thrombi. However, it is impossible to state at this time whether or not such changes are a result of increased pulmonary artery flow or develop as a result of other factors; in some cases rises in left intra-auricular pressure may be the cause for the increased pulmonary resistance.

BELLET.

Loewe, L., Hirsch, E., Grayzel, D. M., and Kashdan, F.: Experimental Study of the Comparative Action of Heparin and Dicumarol on the In Vivo Clot. J. Lab. & Clin. Med. **33**:721 (June), 1948.

Clotting was induced in the jugular veins of adult rabbits. Nine to fourteen days after the induction of thrombosis, heparin and Dicumarol were administered to alternate animals. Sufficient amounts of anticoagulant were given to maintain either the coagulation time or the prothrombin time well above clinically accepted limits. The anticoagulants were administered for two weeks.

The authors found that in the presence of heparin all clots underwent resolution if they were in the sludge stage. Dicumarol did not produce this response because of the time lag between the administration of the drug and the effective prolongation of the prothrombin time. However, beyond this initial stage, both anticoagulants effectively caused resumption of clinical patency in a considerable number of veins which were occluded by clots for four days or longer, even up to two weeks. This effect is at variance with the commonly accepted knowledge of thrombus behavior. The degree of recanalization appears to be greater with heparin. On the basis of this comparative study it would appear that heparin is superior to Dicumarol as an anticoagulant agent.

KLINE.

Horlick, L., and Katz, L. N.: The Effect of Diethylstilbestrol on Blood Lipids and the Development of Atherosclerosis in Chickens on a Normal and Low Fat Diet. J. Lab. & Clin. Med. **33**:733 (June), 1948.

The implantation of stilbestrol pellets in young chickens resulted in a marked hyperlipemia and hypercholesterolemia while on a normal diet and on a specially prepared low fat diet. After stilbestrol implantation, chickens on the normal diet developed a somewhat higher cholesterolemia than did the chickens on the low fat diet. Atherosclerosis of the induced type was observed in a high proportion of the stilbestrol-treated chickens in both the group receiving the normal diet and the group receiving the low fat diet. Spontaneous atherosclerosis occurred in 40 per cent of the chickens used as normal controls, but it occurred in none of the control group which was placed on a low fat diet. The authors state that stilbestrol probably acts to produce atherosclerosis through its cholesterolemic effect.

KLINE.

Slaughter, O. L., Brown, H. S., and Wakim, K. G.: Effects of Tetraethylammonium Chloride on Blood Flow in the Extremities of Man. J. Lab. & Clin. Med. **33**:743 (June), 1948.

The purpose of this study was to determine the effect of tetraethylammonium chloride on the blood flow in the upper and lower extremities of healthy human subjects exposed to relatively warm environment (temperature ranging between 80° and 85° F.) and to establish a basis for comparison with subsequent studies on various abnormalities of the vascular system in patients.

Tetraethylammonium chloride was given intravenously to seven healthy adults. The effects of the drug were studied plethysmographically by the use of the compensating spirometer recorder. In the presence of vasodilatation due to a relatively warm environment of 80° to 85° F., tetraethylammonium chloride produced an average increase in blood flow of 100 per cent in the forearms and 135 per cent in the legs. In addition to the increase in blood flow, disturbances of vision with impairment of accommodation, metallic taste and dryness of the mouth, and increase in heart rate occurred after injection of tetraethylammonium chloride.

KLINE.

Fastier, F. N., and Smirk, F. H.: Some Properties of Amarin, With Special Reference to Its Use in Conjunction With Adrenaline for the Production of Idio-ventricular Rhythms. J. Physiol. **107**:318 (June), 1948.

The circulatory effects of Amarin, a cyclic amidine derivative, were studied in dogs by a number of mechanical devices, including motion pictures, electrograms, myocardiographs, oscillography, etc., and by direct observation. This compound causes a profound bradycardia with lengthening of the P-R and QRS-T durations, occasionally to three times the normal, by a nonvagal effect. In larger doses the heart beat may originate from the A-V node or from a ventricular focus. Various types and degrees of heart block were noted, as were such abnormalities as the independent contraction of the auricles, the driving of the auricles by the ventricles, electrical alternation, and changes in S-T segment and T waves. Small doses exert a pressor action by peripheral vasoconstriction. Larger doses may produce circulatory collapse with cardiac dilatation and arrest.

After Amarin the pressor responses to small doses of epinephrine are greatly increased in the anesthetized animal. Ventricular flutter could be readily produced by moderate doses of epinephrine. When this was observed directly, a series of peristalsis-like waves succeeded each other over approximately the same course on the ventricular surface; two or three waves could be seen at one time and these did not originate from any single point. It would seem that the refractory period was shortened, and flutter would develop after a new excitatory wave began before the preceding ventricular wave had ended. Just before flutter develops, one may see an R wave superimposed on a T wave. This is probably an extreme instance of an increase in duration of ventricular systole relative to that of diastole.

Under Amarin, ventricular fibrillation appeared as many small wavelets running in different directions. Many regions of the ventricles showed regular cycles of mechanical movement which

were not necessarily repeated in the same direction, nor were they of equal strength. Thus, ventricular fibrillation, under these conditions, did not appear to depend on any simple system of circus rhythms. Flutter induced by Amarin and epinephrine was probably due to multiple circus rhythms.

WAIFE.

Konzett, H., and Verney, E. B.: Observations on the Urine, Blood and Arterial Pressure of Dogs Before and After the Production of Renal Ischemia. J. Physiol. **107**:336 (June), 1948.

These investigators were unable to confirm the report of Lockett (J. Physiol. **105**:126, 1946) that a new base, termed *x*, was present in the urine of dogs after the production of renal ischemia. Lockett claimed that this base is absent in normal animals, that it appears in the urine within ten minutes following renal artery compression, that it is excreted mainly by the normal renal cortex, and that a clear relation exists between the presence of this substance and hypertension. On the contrary, these authors found that a color test for the *x* substance was positive in normal urine, and no increase was noted after renal artery obstruction. Piperidine in the dog's urine gives the same color reaction as the postulated *x* substance.

WAIFE.

Ogilvie, T. A., Penfold, J. B., and Clendon, D. R. T.: Gangrene Following Intra-arterial Injection of Myanesin. Lancet **254**:947 (June 19), 1948.

A 67-year-old woman was admitted to the hospital with a provisional diagnosis of neoplasm of the stomach. Laparotomy revealed a gall bladder with thickened walls surrounded by many adhesions and cholecystectomy was performed. During the operation 10 ml. of 10 per cent Myanesin was injected into the median basilic vein to obtain muscular relaxation. The same day the right forearm and hand were much discolored, deeply cyanosed, and of marble coldness; but a good radial pulse was easily palpable at the wrist. A brachial plexus block was performed with procaine, but the circulation did not improve. Next day the hand and forearm were still blue, cold, and functionless, although there was a good radial pulse. A cervical sympathetic block was done, but though the fingers may have been slightly warmer for a short time, after this procedure they were still deeply cyanosed.

Two days later the arm was blue, cyanosed, and cold from the finger tips to the elbow, the nails being almost black. The brachial artery was exposed opposite the elbow joint; the wound bled freely above the elbow, but did not bleed below the joint level, and the superficial veins were collapsed. No thrombosis was present in the brachial, radial, or ulnar artery. The gangrene of the hand and forearm progressed, but the patient's general condition gave no cause for anxiety. The arm was amputated three inches above the elbow joint. The upper end of the brachial artery showed unorganized ante-mortem thrombus attached to the intima.

Subsequent experimental studies revealed that the curdling observed was not due to the effect of Myanesin on the blood, plasma, serum, or heparin, but that there was an alteration in the physical state of the Myanesin with its subsequent precipitation from solution by some constituent or constituents of the blood. It is possible, therefore, that the gangrene in this case can be explained by the profound change which takes place when blood and Myanesin are mixed.

It is possible that, in spite of adequate skill and care in making the injection, some of the solution was injected into the brachial artery instead of into the median basilic vein.

BELLET.

American Heart Association, Inc.

1775 Broadway, New York 19, N. Y.
Telephone Plaza 7-2045

TRAINING SCHOOL FOR CARDIOVASCULAR INVESTIGATORS

A twelve months' training course in the disciplines of cardiovascular research for a limited number of qualified individuals will be offered with the support both of the American Heart Association and the National Heart Institute, United States Public Health Service. If the enrollment warrants, the course will begin July 1, 1949; otherwise, Sept. 1, 1949. For details write: Dr. C. J. Wiggers, Director of the Department of Physiology, School of Medicine, Western Reserve University, Cleveland, Ohio.

Purpose.—To accelerate the development of available qualified personnel for prosecution of research in cardiovascular problems.

Scope.—A year's planned training consisting of:

1. Formalized technical training in various research methods employed in cardiovascular studies on human subjects and animals (eight weeks).
2. Experimentation apprenticeship. Assistance of qualified investigators in basic animal research. Associate Professors Opdyke and Selkurt. Assistant Professors Alexander and Brecher will head such research groups (eighteen weeks).
3. Independent research. Supervised experience in selection and attack of a problem in basic cardiovascular research, assessment of previous work, planning of experimental approach, critical evaluation of experimental data, etc. (sixteen weeks).
4. Preparation of manuscript. Supervised experience in writing a paper (six weeks).

JOINT PROJECTS

The Board of Directors of the American Heart Association has approved a budget of $21,500 for a joint project to be undertaken by the National Heart Institute and the American Heart Association in the field of education. The project calls for professional and public educational materials and programs currently available and in use by medical schools, medical societies, research organizations, health departments, and voluntary health agencies. The study will examine the further needs of these groups and will analyze the extent to which these materials satisfy existing needs. Materials which are found to be worth while will receive more intensive promotion to encourage wider distribution and use.

It was recommended that the American Heart Association and the National Heart Institute collaborate with industry and labor in exploring the possibilities for an industrial program. The study will determine the opportunities for such a program, its objectives, and the methods of approach to be adopted.

The Board of Directors also approved a grant of $7,500 for a heart disease education program for registered pharmacists to be undertaken in collaboration with the American Pharmaceutical Association and the National Heart Institute. The project is identical with that now being carried out in regard to cancer under a special grant from the National Cancer Institute. The new activity will begin at the conclusion of the cancer project and will place total emphasis on heart disease during the ensuing year.

The project envisions a series of bimonthly mailings to approximately 15,000 pharmacists in the United States, thus supplying educational material on the early symptoms of heart disease and on heart disease control.

Through this educational activity, the pharmacist will receive essential information concerning the heart diseases. As adviser to persons who see him before consulting their physicians, he will have better information whenever inquiries from the public reveal possible symptoms of heart disease. This will facilitate early referral of patients.

The bimonthly bulletins will be designed for posting in the prescription room. Each mailing will include a display card addressed to laymen. The cards will be informational in character and carry a "see your doctor" message to approximately 3,000,000 people who visit the pharmacists cooperating in this project.

The program calls for wide educational publicity in pharmaceutical journals, and for radio scripts and transcriptions for the use of local and state pharmaceutical associations. The American Heart Association will be consulted in the planning of the project and the preparation of all educational materials.

PROCEDURE FOR AFFILIATION OF LOCAL AND STATE ASSOCIATIONS

It is recommended that local or state Associations observe the following procedure in requesting affiliation with the American Heart Association:

1. Forward a letter to the American Heart Association acknowledging that the affiliate intends to abide by the formula for affiliation, as outlined by the American Heart Association.

The listing in that letter of the duly elected officers and the signing of that letter of application by two of those officers.

Specific description of the area of operation also to be included in this letter.

2. The submission of Statement of Purposes and By-Laws.
3. Submission of tentative budget and plan of operation for the succeeding year.
4. Nominations for the Assembly. Notify the President or other responsible officer that his affiliated Heart Association is entitled to a specified number of delegates to the Annual Assembly and that he is requested to make suggestions for nominations and send it out to us for reference to the Nominating Committee.

PROGRAM

TWENTY-SECOND SCIENTIFIC SESSIONS

AMERICAN HEART ASSOCIATION

JUNE 3, 4, 1949

VERNON ROOM, HADDON HALL, ATLANTIC CITY, N. J.

FIRST SESSION

Friday, June 3, 1:30 P.M.

Chairman: Norman E. Freeman, Chairman, Section on Circulation
Secretary: Grace M. Roth

1. THE EFFECTS OF DIHYDROERGOCORNINE ON THE GENERAL CIRCULATION OF HYPERTENSIVE AND NORMOTENSIVE SUBJECTS. JOSEPH H. HAFKENSCHIEL, CHARLES W. CRUMPTON, JOHN H. MEYER, AND WILLIAM A. JEFFERS, PHILADELPHIA, PA.
2. SYMPATHETIC VENOCONSTRICTOR REFLEXES IN MAN. JULIUS LITTER AND ROBERT W. WILKINS, BOSTON, MASS.
3. STUDIES OF THE PULMONARY AND SYSTEMIC ARTERIAL PRESSURE IN CASES OF PATENT DUCTUS ARTERIOSUS WITH SPECIAL REFERENCE TO EFFECTS OF SURGICAL LIGATION. B. E. TAYLOR, A. A. POLLACK, H. B. BURCHELL, O. T. CLAGETT, AND E. H. WOOD, ROCHESTER, MINN.

4. GEORGE BROWN MEMORIAL LECTURE. WALTER H. SEEGERS, WAYNE UNIVERSITY COLLEGE OF MEDICINE, DETROIT, MICH.
5. SYNTHETIC RATIONS IN THE STUDY OF DIETARY FACTORS IN EXPERIMENTAL RENAL HYPERTENSION IN THE RAT. PHILIP HANDLER AND F. BERNHEIM, DURHAM, N. C.
6. ARTERIOSCLEROSIS AND PYRIDOXINE DEFICIENCY. J. F. RINEHART AND L. D. GREENBERG, SAN FRANCISCO, CALIF.
7. RELATIONSHIP BETWEEN PROTHROMBIN TIME AND PLASMA LEVELS OF DICUMAROL. MURRAY WEINER, SHEPARD SHAPIRO, JULIUS AXELROD, AND BERNARD B. BRODIE, NEW YORK, N. Y.
8. EPINEPHRINE AND NOR-EPINEPHRINE IN PHEOCHROMOCYTOMA. MARCEL GOLDENBERG AND HENRY ARANOW, JR., NEW YORK, N. Y.
9. HEPATO-RENAL VASOTROPIC FACTORS IN ESSENTIAL HYPERTENSION AND IN ECLAMPSIA. EPHRAIM SHORR AND BENJAMIN W. ZWEIFACH, NEW YORK, N. Y.
10. THE MECHANISM OF SOME ANTIDIURETIC RESPONSES AND THEIR RELATIONSHIP TO THE SODIUM RETENTION OF CONGESTIVE CARDIAC FAILURE. B. C. SINCLAIR-SMITH, J. H. SISSON, A. GENECIN, A. KATTUS, C. MONGE, AND E. V. NEWMAN, BALTIMORE, MD.
11. THE EFFECT OF DIGOXIN IN LEFT VENTRICULAR FAILURE. M. IRENE FERRER, REJANE M. HARVEY, RICHARD T. CATHCART, ANDRE COURNAND, AND DICKINSON W. RICHARDS, JR., NEW YORK, N. Y.

SECOND SESSION

Saturday, June 4, 9:00 A.M.

Chairman: Tinsley R. Harrison, President, American Heart Association

Secretary: John J. Sampson

12. THE TREATMENT OF COARCTATION OF THE AORTA. ROBERT E. GROSS, BOSTON, MASS.
13. COMMISSUROTOMY FOR MITRAL STENOSIS. CHARLES P. BAILEY, ROBERT P. GLOVER, AND THOMAS J. O'NEILL, PHILADELPHIA, PA.
14. THE NATURE AND TREATMENT OF AURICULAR FLUTTER. MYRON PRINZMETAL, ELIOT CORDAY, ALVIN L. SELLERS, WALTER A. FLIEG, AND H. E. KRUGER, LOS ANGELES, CALIF.
15. CATHETERIZATION OF THE LEFT HEART IN MAN. HENRY A. ZIMMERMAN, ROY W. SCOTT, AND NORMAN O. BECKER, CLEVELAND, OHIO.
16. THE VECTORAL INTERPRETATION OF PRECORDIAL T-WAVE INVERSION. ROBERT P. GRANT, ATLANTA, GA.
17. QRS-T PATTERNS IN THE PRECORDIAL LEADS THAT MAY BE MISTAKEN FOR MYOCARDIAL INFARCTION. GORDON B. MYERS, DETROIT, MICH.
18. THE SYNDROME OF ACUTE MYOCARDIAL INFARCTION ASSOCIATED WITH EARLY ELECTROCARDIOGRAPHIC FINDINGS SUGGESTIVE OF PREDOMINANTLY SUBENDOCARDIAL INJURY, WITH OBSERVATIONS ON THE "TOUCH EFFECT" OF THE CARDIAC CATHETER. HANS H. HECHT, LEONARD W. RITZMANN, AND MARGUERITE GREAVES, SALT LAKE CITY, UTAH.
19. THE SUBCUTANEOUS USE OF THIOMERIN, A NEW MERCURIAL DIURETIC FOR TREATMENT OF CONGESTIVE HEART FAILURE. ROBERT G. BATTERMAN, DAVID UNTERMAN, AND ARTHUR C. DE GRAFF, NEW YORK N. Y.

Saturday, June 4, 12:00 P.M.

Annual Business Meeting of Members

THIRD SESSION

Saturday, June 4

Panel Discussions

Chairman: Eugene A. Stead, Jr., Chairman, Program Committee

1:30 P.M.

1. MANAGEMENT OF CONGESTIVE FAILURE AND IMPORTANCE OF LOW SODIUM DIET.

George E. Burch, New Orleans, *Chairman*
William Dock, New York
Walter Kempner, Durham
Samuel Proger, Boston
Ferdinand Schemm, Great Falls
James Warren, Atlanta

2:35 P.M.

2. CONGENITAL HEART DISEASE.

Alfred Blalock, Baltimore, *Chairman*
Richard Bing, Baltimore
Louis E. Martin, Los Angeles
Edward Neuhauser, Boston
Helen Taussig, Baltimore

3:40 P.M.

3. ANTICOAGULANT THERAPY.

Edgar V. Allen, Rochester, *Chairman*
Louis N. Katz, Chicago
I. S. Ravdin, Philadelphia
Walter H. Seegers, Detroit
Geza de Takats, Chicago
Irving S. Wright, New York

You are invited to forward a question or topic which you would like to have discussed at any of these panels to the American Heart Association, 1775 Broadway, New York 19, N. Y.

Saturday, June 4, 7:00 P.M.

Annual Dinner

Vernon Room, Haddon Hall

PROGRAM COMMITTEE

Chairman: Eugene A. Stead, Jr., Durham

Graham Asher, Kansas City
James A. Greene, Houston
John Hepburn, Toronto
Louis N. Katz, Chicago
Robert L. King, Seattle
William G. Leaman, Jr., Philadelphia
Robert Bruce Logue, Atlanta
Louis E. Martin, Los Angeles
Benedict Massell, Boston
Hugh Montgomery, Philadelphia
Robert M. Moore, Indianapolis
Francis F. Schwentker, Baltimore
Roy W. Scott, Cleveland
Arthur P. Selzer, San Francisco
Morse J. Shapiro, Minneapolis
F. Janney Smith, Detroit
Harold J. Stewart, New York

INTERIM CAMPAIGN REPORT

Local affiliates and committees have reported campaign collections of approximately $2,100,000, as of March 21, 1949. This figure represents incomplete returns from 157 groups. Reports from 204 groups have yet to be received.

Of this amount, more than $100,000 was received at National Headquarters of the American Heart Association as the result of national radio and newspaper publicity, activity of cooperating service groups and fraternal organizations, and the distribution of plastic hearts and Save-a-Heart banks. Only a small fraction of plastic hearts and banks have been returned to National Headquarters. A considerable return is expected from these sources, especially the plastic hearts which average more than $6.25 per heart.

Final figures on the results of the 1949 campaign are not expected until May or June of this year. Complete reports from local groups will not be available for several months, and it would be premature to estimate the total national collection at this time.

It is of interest that a total of more than 7,000,000 pieces of printed literature were ordered; over 240,000 plastic hearts and 1,260,000 Save-a-Heart banks were distributed by the end of the campaign period.

A significant feature of the drive has been the rapid growth of committees in local areas. Enlistments of Campaign Chairmen and Co-chairmen increased from 174 on January 29 to 743 by the end of the campaign.